The American Journal of

DIGESTIVE DISEASES AND NUTRITION

The Official Publication of

THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

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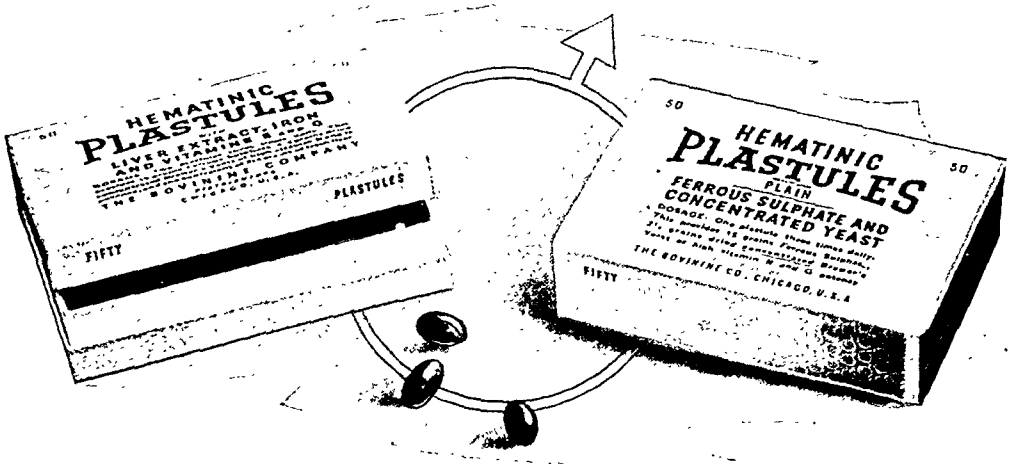
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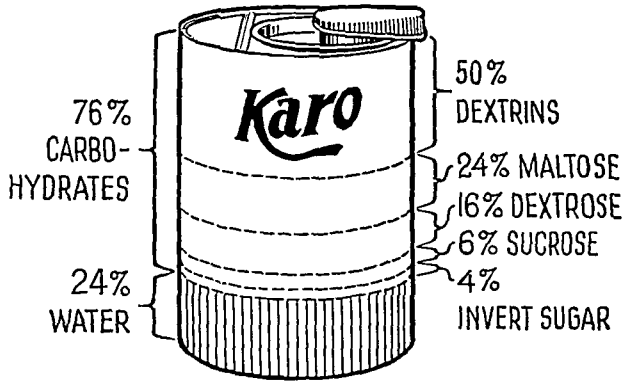
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VITAMIN REQUIREMENTS OF MAN

III. VITAMIN A

• The importance and multiple functions of vitamin A in human nutrition are widely dealt with in clinical literature. Xerophthalmia resulting from severe vitamin A deficiency is rare in this country, yet the etiology of many pathogenic conditions, namely, night-blindness, urinary calculi, lesions of the nervous system, impairment of epithelial tissue and subnormal growth, has been linked with chronic avitaminosis A (1).

Minimum human requirements for vitamin A are influenced by such variables as size of the individual and efficiency of absorption. The minimum daily requirement of infants has been estimated at 1500 International units, based upon the vitamin A content of milk. The need for the vitamin is not supplied by 1200 International units, while 2000 International units appear to be sufficient (2).

Although the minimum requirement of the adult has been estimated to be as low as 500 International units, the optimum level for both older children and adults is probably between 3000 and 5000 International units per day (3). The League of Nations Technical Commission recommends over 5000 International units of vitamin A for the pregnant and for the lactating woman (4).

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(3) a 1934 J Am Diet Assn 10,296
b 1936 Indian J Med Research 23, 741

(4) 1936 League of Nations Report on Physiological Bases of Nutrition, League of Nations Publication Department, Geneva

(5) 1933 Chemistry of Food and Nutrition H C Sherman 4th Ed Page 364 MacMillan New York

(6) a 1931 J Nutrition 4, 267
b 1933 J Am Diet Assn 9, 295

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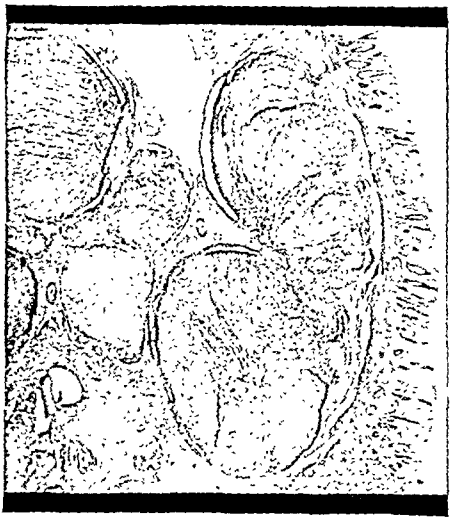
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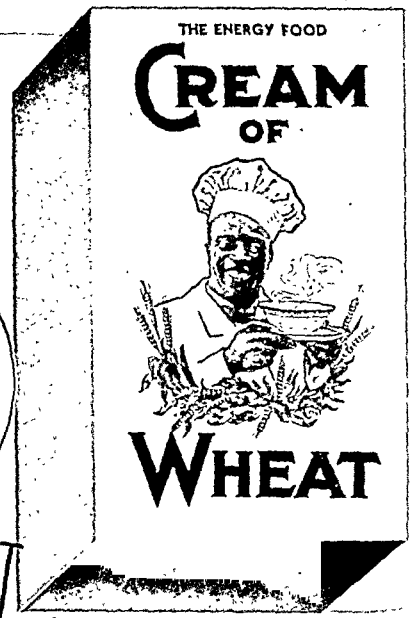
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CANNED FOODS IN THE CONTROL OF SUBACUTE DEFICIENCIES OF THE ANTI-PELLAGRIC FACTOR

As a result of his classical researches, Goldberger first proposed the name "Pellagra-Preventive Factor" for that component of the vitamin B complex which he found effective in the prevention of human pellagra. Subsequently, the terms vitamin "G" and sometimes vitamin "B_2" were used to designate this effective factor. However, until biochemical research has conclusively established its identity, it is now apparent that we had best return to Goldberger's original designation for that entity which protects the human against pellagra.

In contrast to the other vitamin deficiencies, cases of severe deprivation of the anti-pellagric factor are not uncommon in certain regions of the United States. It is also known that if the intake of food be drastically restricted for some reason—alcoholism, for example—pellagra may be encountered in localities in which the disease is not endemic (1). For these reasons, it is not unreasonable to suspect that subacute or latent deficiencies of the P-P factor may also be existent in this country.

In the absence of typical dermatitis, available means for the diagnosis of deficiencies of the anti-pellagric factor are not entirely satisfactory. The practitioner must rely upon a variable group of less specific symptoms such as glossitis, diarrhea, digestive disturbances, and nervous and mental disorders. However, consideration of these symptoms along with an evaluation of the diet upon which the subject had been maintained, may permit the conclusion that suboptimal intake of the P-P factor should be suspected.

The treatment of severe or perhaps even the mild manifestations of this dietary deficiency may require intensive therapy with food products or preparations known to be rich in the pellagra preventing factor. However, prevention of pellagra and maintenance of the cure appear to be largely matters of dietary regulation. In this connection, commercially canned foods deserve particular mention.

Goldberger and his associates directed considerable attention to evaluation of the pellagra-preventive powers of common foods. The values of foods, many of them canned foods, in the prevention of pellagra have been determined (2) by investigations in which human subjects were used.

In view of these facts, it is apparent that certain commercially canned foods will prove reliable, convenient and economical in the formulation of diets calculated to protect against mild or severe deficiencies of the P-P factor.

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1937 J Am Med. Assn. 108, 15.
1935. Ibid. 104, 1377.

2. 1934. U. S. Pub. Health Rpts. 49, 755.

This is the thirty-fifth in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.

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Dietary Principles in the Treatment of Gastro-intestinal Diseases*

By

ALBERT F. R. ANDRESEN, M.D., F.A.C.P.†
BROOKLYN, NEW YORK

"BE careful of your diet"! How often is this the only dietary prescription given to a sufferer from gastro-intestinal symptoms! If the patient insists on details, he is told to avoid "greasy" foods, "acid" foods, "sweets," red meats" or "starchy" foods, or perhaps is advised against partaking of some food to which the doctor has a pet aversion or an actual idiosyncrasy. When conditions do not improve, is it any wonder that patients seeking detailed instructions based on definite principles, consult the quacks and charlatans who in recent years, in spite of the depression, have been doing a tremendous business, although their theories are fantastic and the results of their treatments in many cases have been disastrous?

The ponderous volumes on dietetics which of late have been published in such profusion have, I believe, done more to confuse the medical practitioner than to help him. If dietetics is such a difficult and controversial subject that it takes one or two thousand pages of text to propound its principles, the average practitioner cannot take the time to make a study of this subject. If the time is available in caring for a given case, search through the books will reveal various, and often entirely different, diets suggested for the disease in question, and a choice will be difficult. If one is decided upon, it means considerable work to make a copy of it for the patient, and when it is all written down some of the foods prescribed may not be tolerated by the patient. This means starting all over again—a task, which, if repeated several times, soon discourages the practitioner from further efforts.

GENERAL DIETARY PRINCIPLES

In order to prescribe a rational diet it is necessary to understand certain principles which must apply to all diets. These principles are well known and need not be discussed here at too great length. They include attention to the caloric value of the food, a proper balance of the essential ingredients, an adequate vitamin supply, a sufficient ash or mineral content and the required amount of indigestible residue and water.

The *caloric value* does not need to be figured out in detail. In fact, in an adult, there are so many factors involved in converting a given number of calories of food ingested into actual available calories in the tissues that a mere statement that a patient is getting two thousand or four thousand calories means very little. The real test as to whether the patient's food contains the required number of calories is the variation in the weight of the patient, and the quantity and type of food will have to be regulated according to this observation.

The *proper balance of the essential ingredients* is often lost sight of when prescribing meat-free, reducing or fat-free diets. Diets deficient in protein are the cause of the debilitated, anemic state of many patients. Insufficient carbohydrate intake supplies inadequate fuel for daily combustion and results in tissue destruction, and insufficient fat, by its failure to stimulate biliary tract emptying, may result in serious gall bladder stasis. The average individual, no matter what his disease may be, requires from sixty to eighty grams of *protein* per day, which must be supplied largely in the form of meat, eggs, cheese, nuts and milk, although a few vegetables, such as beans and peas also contain small amounts of protein. The *carbohydrate* ration, supplied in the form of sugar and the starch of cereals, vegetables and fruits, must depend on the patient's weight and on certain metabolic factors, such as a diabetic state. Where energy must be rapidly supplied, or where liver disease is present, dextrose can be given by mouth, being used in place of saccharose in drinks or other feedings. The *fat* content, also to be governed by the patient's weight, is supplied in the form of butter, meat-fats and oils.

Vitamin deficiency has recently been shown to be the cause of many previously obscure conditions. It seems to play a part in the production of the arthritides, various gastro-intestinal disorders, genito-urinary diseases, and nervous disorders, as well as the previously recognized deficiency states. Ordinarily it may be stated that a diet containing milk, eggs, butter, green vegetables (raw and cooked), raw fruits and whole grains supplies an adequate vitamin supply, but it is probably better, especially during the winter months, to add some extra concentrated vitamin products to the diet of patients whose symptoms might be influenced by vitamin deficiency. Cod or halibut liver oils, viosterol and yeast are usually sufficient.

The *mineral content*, including particularly iron, phosphorus and calcium, is also supplied by the foods mentioned in the discussion of the vitamins, but individual cases may require the addition of an extra supply of one or more of these substances.

Water is one of the most frequently neglected parts of a diet. At least six or eight glasses per day are required to encourage gastro-intestinal digestion and absorption, to supply the water content of the urine, sweat and respiratory tract moisture, and to provide sufficient liquid to keep the feces from becoming too dehydrated.

Indigestible material or *roughage*, including leafy vegetables, skins, pulps and seeds of fruits and hulls of grains, are necessary to provide bulk for the feces. An insufficient quantity of roughage normally results in infrequent bowel movements and should not be the signal for the use of cathartics. Where smooth bulk is desirable, agar or some other similar substance may be added to the diet.

*From the Department of Medicine, Long Island College of Medicine.
†Clinical Professor of Medicine; Chief of the Department of Gastroenterology.
Submitted December 21, 1936.

MECHANICAL EFFECTS OF DIET

In gastro-intestinal diseases great help can be obtained from the diet by considering the mechanical effects of the food on the gastro-intestinal tract. These effects can best be discussed under four headings, as follows:

1. *Soothing* or *irritating* effects must be considered. In cases where the gastro-intestinal mucosa is in an irritable condition as a result of ulceration, inflammation or recent poisoning, a smooth, soothing, emollient diet would be indicated, and such foods as milk, cream, cheese, eggs, well-cooked cereals and puddings, ice cream and gelatin and a minimum supply of condiments should be combined into a well-balanced diet. In cases where the gastro-intestinal tract is in a sluggish or atonic state, as after protracted illness and rest in bed, it may be desirable to combine with the nutritious, well-balanced diet some irritating foods, including meat extractives, condiments, the whole grain cereals and breads, the skins and pulps of fruits and the leafy vegetables.

2. The *bulk* of the diet is important, not only the initial bulk of the feedings but also the bulk of the indigestible residue. Where the stomach is dilated and atonic, small, frequently repeated feedings, by encouraging greater contraction of the stomach in order to empty itself, will often rapidly restore the tone of such an organ. On the other hand, the active, tonic stomach of reflex pylorospasm with retrostalsis can often be made to quiet down by large though soothing feedings, which, if vomited, must be immediately repeated. The bulk of the indigestible materials or roughage must be guided by conditions in the colon. In acute, irritative, ulcerative conditions of the colon a low bulk would be indicated, and a diet almost free or roughage would be desirable. In both the hypertonic or spastic colon as well as in the atonic colon, bulk is indicated, thus giving the colon a definite task to perform, tending to restore normal function. In colonic adhesions and kinks the high-residue diet, by keeping the colon more solidly filled, will prevent symptoms often due to small masses of inspissated feces attempting to pass a narrow point and getting stuck because of insufficient *vis a tergo*. In diverticulosis also, bulky colonic contents will prevent the entrance of irritating liquid material into the diverticula.

3. The *consistency* of the food must be modified according to the conditions present in the esophagus and stomach. Where there is an organic narrowing, cicatricial or malignant, the food should be of a soft or liquid consistency, in order to pass the narrow point. A well-balanced diet, in liquid form, containing milk, cream, eggs, lactose or glucose, cereal gruels and fruit juices, will pass through an almost obstructed esophagus or pylorus and will so improve the patient's general condition that operative or other necessary procedures will no longer be too great a risk. On the other hand, in spastic conditions, such as so-called cardiospasm and pylorospasm, firm, even dry food will often pass the spastic area when liquids would be regurgitated.

4. The *temperature* of the ingested food is of some importance. It must be remembered that the stomach can bring the temperature of ingested cold materials up to body temperature more efficiently and quickly than it can reduce the temperature of hot foods. Liquids, such as beverages and soups, rapidly swallowed and reaching the stomach at excessively high temperatures, are undoubtedly extremely irritating, and in cases of gastric cancer a history of the habit of taking hot liquids is so frequently elicited, that we must consider this source of chronic irritation as a possible etiologic factor. On the other hand, iced drinks or plain ice, in being warmed by the stomach walls, call for a sudden and marked influx of blood and are therefore definitely contraindicated during or soon following a gastric hemorrhage. Cold drinks also, by stimulating peristalsis, sometimes aggravate a diarrhea.

PHYSIOLOGICAL EFFECTS OF DIET

A consideration of the physiological effects of diet is of the greatest importance. The effects of diet on the function of the *esophagus*, for instance, is illustrated by the fact that in the normal esophagus liquids pass more rapidly along its length and into the stomach than solids, whereas in so-called cardiospasm, relaxation of the cardia is encouraged more by solid foods. In the case of the *stomach*, both motility and secretion are affected. Hunger contractions, occurring when the stomach is empty, and markedly increased when ulceration is present in the stomach and duodenum, then becoming perceptible as hunger pains, are relieved by filling the stomach—and keeping it filled—by frequent feedings. Retrostalsis, a more or less mild reverse peristalsis, occurring as a result of irritation of the gastro-intestinal tract from within or without, from stomach to anus, such as ulcer, gall bladder disease, appendicitis, colitis, pelvic conditions or even fissures or hemorrhoids, producing spasm and resulting in the symptoms of epigastric distress, fulness, heartburn, sour eructations, sour regurgitation or even vomiting, is relieved by frequent bulky feedings, which produce more powerful downward peristalsis to overcome the reverse waves. Such a diet would not be successful in actual obstruction, and is often of value as a method of differential diagnosis between spasm and obstruction. In gastric irritability, with increased and prolonged acid secretion, foods which combine readily with hydrochloric acid or do not overstimulate its production, are indicated. Such foods would include milk, eggs, cereals and fats. In the absence of acid secretion, foods which require the action of pepsin-hydrochloric acid on the protein envelopes of their individual cells or fibers, such as uncooked starch and meat, should be avoided or should be properly prepared by adequate cooking or maceration. There is considerable doubt whether condiments or meat extractives will have any effect in stimulating gastric secretion where this is entirely absent, and their irritating effect on the mucosa may easily be detrimental in cases where the anacidity is due to a gastritis. Dilute hydrochloric acid, added to the diet, is of some use in stimulating pancreatic secretion, but is practically of value only in cases where diarrhea accompanies the achylia. It must be remembered that milk, when taken alone, is curdled by the gastric juice into large lumps, whereas when modified by the addition of starch in the form of infant foods or crackers, bread or cake, the curds are small and easily and quickly digested. Gelatin, which acts as a non-irritant protein food, is of value in promoting blood coagulation, and should be remembered in prescribing for cases of gastric hemorrhage.

Biliary tract function can be materially affected by diet. Any foods, but particularly fats, passing through the duodenum, cause relaxation of the sphincter of Oddi at the papilla of Vater, and resultant contraction and emptying of the gall bladder. In conditions of biliary stasis, therefore, frequent feedings, with adequate fat content (preferably not the fat of meat or fowl) tend to clear the biliary tract and tone up the gall bladder musculature. The hypothesis that certain specific foods have more effect on actually promoting liver secretion than have others has not been conclusively demonstrated; any good mixed diet would be of value in this respect. Where there is actual liver damage, animal experiments have demonstrated the extremely harmful effects of meat and meat extractives and the beneficial effects of high carbohydrate feedings. In severe cases, large doses of glucose, orally or parenterally administered, are indicated, and sometimes increasing the tolerance to sugar by the use of insulin is of value.

On *colonic* motility, diet may have either a positive or a negative effect. If a diet free from residue is taken, there will be no effect. Indigestible constituents of the diet, if coarse and irritating, as is bran, will stimulate and improve peristalsis; if smooth and soothing, as is agar, will allay irritation and encourage normal motility. In cases with acutely inflamed, ulcerated and irritable bowels, therefore, a non-residue diet is indicated, whereas in chronic, spastic, irritable conditions, a smooth bulk is desirable, and in atonic conditions, a coarser bulk would be preferable. The bacterial flora of the colon, normally showing almost daily variations, is influenced by the character of the food; a predominance of the acid-forming bacteria occurring in high carbohydrate diets, and of putrefactive bacteria (coli group) in high animal protein diets. It is questionable whether changing the intestional flora is of any value in disease.

ALLERGIC CONSIDERATIONS

Any diet which does not take into consideration the individual idiosyncrasis or the allergic reactions of a patient will usually prove to be inadequate. Most individuals have at least a few of such peculiarities, and if the physician entirely disregards a patient's statements in respect to likes and dislikes may result in embarrassing failure to allay or modify symptoms by diet. It is true that neurotic patients often imagine that certain foods are "bad" for them, when such would really be of value. However, if it is known that a food invariably will produce a skin rash, heartburn, sour regurgitation, an attack of migraine, abdominal cramps or diarrhea, it is well to avoid such a food in prescribing a diet. On the other hand, if a patient is known to be following conscientiously a diet which should produce definitely beneficial results, and these results are not obtained in due time, a suspicion of food allergy must be engendered and search for the food to which the patient is sensitized must be carried out by means of diet study or skin reactions, preferably the former. A readjustment of the diet in accord with information thus obtained will often produce startling results.

PRACTICAL APPLICATION

As examples of the application of the principles which we have been discussing to actual disease conditions, a few typical diets will be presented. In each diet a proper balance of ingredients is an essential consideration.

In uncomplicated *peptic ulcer*, the stomach is irritable, it tends to contract forcibly, making the hunger contractions recognizable to the patient as pain, and there is a tendency to a continued secretion of a hyperacid gastric juice. The diet, therefore, should be bland and smooth, there should be frequent feedings in order to prevent the stomach from becoming empty and the food should combine readily with acid and not too greatly stimulate its secretion. The following diet is the result of the application of these principles:

PEPTIC ULCER DIET

Breakfast:
(8 A. M.)
Milk—1 glass (preferably, the milk should be heated)
Cereal—cooked—3-6 ounces
Egg—one—soft boiled or poached
Bread and butter (or toast)
Juice of orange or grapes (at end)

10:30 A. M.
Milk—1 glass
Crackers, bread and butter or plain cake.

Luncheon:
(1 P. M.)
Milk—1 glass
Eggs or cream cheese
Potato, baked or mashed, or spaghetti (without sauce)
Bread and butter
Pudding, custard, jello or ice cream

3:30 P. M.
Milk—1 glass
Crackers, bread and butter or plain cake.

Supper:
(6 P. M.)
Same as luncheon or breakfast.

8:30 P. M., and at 2 or 3 hour intervals after this if awake:
Milk—1 glass
Crackers, bread and butter or plain cake.

Additions

Yeast may be given early in morning or with meals.
Other vitamine preparations, especially vitamine D, are often indicated.
Iron preparations should be added in anemic patients.
Cream and lactose, glucose or other powdered foods may be added to milk or cereal where patient is underweight.
Olive or cottonseed oil before meals is of value in most cases.
Water, at least 6 or 8 glasses per day, is desirable.

In *Gall Bladder Disease*, the gall bladder is sluggish in its contractions and there is a tendency to stasis of its contents, with increased concentration. Duodenal and gastric retrostalsis produce the distressing dyspeptic symptoms. The dietary indications, therefore, are for normal or excessive fat content, with frequent feedings to act as a stimulant to more complete and *frequent gall bladder* emptying, and fairly large quantities to overcome the retrostalsis. Owing to the

usual liver damage, meat and meat extractives are contraindicated. These principles are fully complied with in the "ulcer diet" and this can be used where an ulcer is coexistent. Otherwise we suggest the following:

GALL BLADDER DIET

Breakfast:
(8 A. M.)
Milk—1 glass (milk, preferably heated)
Cereal—cooked—with cream
Egg—one
Bread and butter or toast
Fruit—raw.

10:30 A. M.
Milk—1 glass
Crackers, bread and butter or plain cake.

Luncheon:
(1 P. M.)
Milk—1 glass
Egg, cream cheese or nuts
Vegetables—cooked—any kind
Salad—any raw vegetables
Bread and butter
Fruit, pudding, jello or ice cream.

3:30 P. M.
Milk—1 glass
Crackers, bread and butter or plain cake.

Dinner:
(6 P. M.)
Same as luncheon.

At bedtime and in night, if awake:
Milk—1 glass
Crackers, bread and butter or plain cake.

Additions

Olive oil and cream are taken with meals, but the quantity must vary according to patient's weight. This is also true of desserts and carbohydrates in general.
Vitamines are usually of value—yeast, fish liver oil preparations and viosterol being the most useful.
In achylia with diarrhea, hydrochloric acid may be indicated.
Water, 6 or 8 glasses per day, is essential.

In *Esophageal* or *Pyloric Stenosis* the narrow lumen will not permit the passage of coarse or bulky foods, yet the secretions are normal and a balanced diet is indicated. The dilated stomach can be stimulated to contract on smaller quantities, frequently repeated, thus restoring its tone. A liquid diet is desirable, and we have the following:

PYLORIC STENOSIS DIET

Feedings at 2 or 2½ hour intervals, each containing
Milk—1 glass
Cream—½ ounce or more
Lactose—½ ounce, or Glucose, ½ to 1 ounce, flavored with chocolate or other flavors as desired.

During a twenty-four hour period there must be added to these feedings:
Eggs—3 or 4 a day
Fruit juice—raw—twice a day
Vitamines—yeast, viosterol, fish liver oils are of value
Minerals—iron and calcium, as indicated
Alcohol—may be added to increase caloric value or as a flavoring.
Water—in esophageal obstruction large quantities are desirable, in pyloric stenosis, in order to avoid increasing dilatation, water should be restricted.

CONCLUSIONS

1. In gastro-intestinal diseases a diet, while essentially prescribed for the purpose of nourishing a patient, must be modified to conform to the required mechanical, chemical and physiological indications.
2. Every diet, and preferably each meal, must contain a proper balance of essential ingredients, a sufficient vitamin and mineral supply, adequate amounts of water, and, unless contraindicated, considerable indigestible residue.
3. The purposes of the diet should be explained to the patient and every detail should be given to him in writing so that misunderstandings or actual errors may be avoided.
4. Changes in the diet should be made only in accordance with certain definite indications, such as gain or loss in weight, variations in symptoms, allergic manifestations and when the causes for which the diet originally was prescribed no longer exist.

The Interrelationships of the Pancreas with Other Endocrine Organs in Diabetes

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IN considering diabetes as an entity, it is customary to think of a deficiency of the insulogenic apparatus, either functional, or caused by actual anatomic changes in the islands. That the problem is not so simple as this has been evident to investigators of the subject for many decades. One has only to recall the frequent incidence of diabetes in connection with acromegaly, the frequency of disturbances of carbohydrate metabolism in hyperthyroidism, the sensitivity to insulin of patients with destruction of the suprarenal glands, the amelioration of diabetes following the menopause, etc., to realize the complexity of these interglandular relationships.

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These are all expressions of some factor aside from insular function of the pancreas which alters the diabetic state either favorably or unfavorably as a result of hypersecretion or hyposecretion of some other gland. For this reason, diabetes is not solely the result of a disturbance of the insulogenic function, but a condition which is affected variably by the direct or indirect action of other organs of internal secretion on the islands of Langerhans.

As the knowledge of this internal interrelationship is being clarified, our understanding of the clinical picture is becoming more complete. Much still remains to be done before we shall be able to utilize all the experimental evidence clinically, but there is good reason to hope for much progress along these lines in the future.

In this summary I have tried to collect some of the facts of this endocrine interrelationship which has a bearing on carbohydrate metabolism. What I have to say does not represent original investigation on my part, and I must apologize that the report is not more complete. In a field which is growing so rapidly, it is practically impossible to keep abreast of all the developments, for new work is being reported almost daily, and what is new today becomes old tomorrow. I have given the references for most of the material, and have quoted freely the statements of some authors, at times interspersing remarks that were pertinent from some other source.

To those working intensively on some phase of endocrine physiology, there will be many gaps in this discussion. For these lapses I hope I may be pardoned, for in a subject as broad as this, one could easily write a book on each separate gland. All that is intended here is a short summary of some of the more recent literature in order to give some indication of the complex interrelationships of the other endocrine organs to the insulogenic function.

THE PITUITARY GLAND

The interrelationship of the pituitary with all the other glands of internal secretion is so well established that it is only to be expected that the pituitary exerts an important influence on carbohydrate metabolism. Since the pituitary also regulates, at least in part, the functions of the liver, the suprarenals and the thyroid gland, each of which also apparently has some direct relation to the regulation of carbohydrate metabolism and pancreatic function, as well as direct relationships to each other, it is obvious that the exact role of the pituitary in these processes is very difficult to fathom. How much of the influence on insulogenesis is direct and how much is accomplished through pituitary influence on other organs is at present almost impossible to determine. I myself feel entirely incapable of interpreting all of the known facts in this connection, and in this short review of some of the clinical and experimental findings I make no attempt to offer any sort of comprehensive explanation.

In *acromegaly* the pancreas often shows degenerative changes of the islands in the pancreas. At other times these are normal. Again, hypertrophy and increase in the number of islands has been reported. (Table 1). According to Atkinson, one-third of acromegalics show glycosuria. The glucose tolerance curve often shows an abnormal rise and a sudden fall into a hypoglycemic level. I performed glucose tolerance tests on fourteen patients with acromegaly (Table 2). Of these 43 per cent yielded a normal curve and 57 per cent a diabetic curve.

A severe diabetes can accompany acromegaly. Some of these patients are reported to be insulin-resistant, and do not react well to dietary restrictions. The sugar excretion can be tremendous, such as is seen in no other disease. (Ravaut, Schmidt, Widal).

Apparently, then, there can be several types of glycoregulatory derangement in acromegaly. There can be real pancreatic diabetes, perhaps due to the excessive output of pancreatropic hormone of the anterior hypophysis. The glycosuria can be caused from a dis-

TABLE I

Pathologic findings in the pancreas in acromegaly-diabetes

Author	Islands of Langerhans: Increase Hypertrophy	Islands of Langerhans: Normal	Islands of Langerhans: Decrease Atrophy	Reference
Ravaut	•			Chauffard: Med. Press, London, 110:142, 1920
Pineles, Hausman and Dalsemarre			•	Sachs, MacDonald: *Arch. Neurol. Psych.*, 13:535, 1925
Hausmann and Dallemarre		•		Borchardt: *Deutsch. med. Wchnschr.*, 54:946, 1928
Benda, C			•	*Berlin klin. Wchnschr.*, 57:1205, 1909
Carrel, Hatchery and Dumont	•			*Bull. et. mem. Soc. med. de hop. Paris*, 35:921, 1913
Marinesco and Paulian	•			*Bull. de l. Acad. d. sci. Paris*
Gray, J.	•			*J. Path. and Bact. Edinburgh*, 32:71, 1929

turbance in the midbrain if the hypophyseal tumor is growing toward the lower part of the brain. In these cases the glycosuria is not excessive and usually is not accompanied by acidosis. In the third place, the carbohydrate disturbance can be of the same nature as it is in hyperthyroidism, if the acromegaly is complicated by a hyperfunctioning thyroid, as the case pictured in Chart 1 would indicate.

The acromegalic patients that I have seen have not been resistant to insulin. In Chart 2, I have depicted two such cases. Both patients were women, one forty-one and the other twenty-one years of age. The response to diet and insulin in both cases was quite prompt. In the first case, a large dosage of insulin was used at first (as much as 70 units a day) which was decreased in a month to 35 units a day. Two years later this patient died in coma as a result of ceasing all treatment. The other patient responded well to insulin and in less than a month all insulin could be discontinued. At the end of a month, the blood sugar was normal, but a glucose tolerance test still showed a diabetic curve. Following this the pituitary was irradiated and repeated checks showed a normal blood sugar level without special diet or insulin.

The third case is extremely interesting. (Chart 3). This patient was a postman, fifty-five years of age, with pronounced acromegaly, who came into the hos-

pital with a fasting blood sugar of 440. He, too, responded promptly to insulin and diet and in less than a month the insulin could be discontinued. Four months later the glucose tolerance test was repeated and was virtually normal. Were one's observations to

TABLE II

Glucose tolerance curves in acromegaly (John)

Type of Curve	Non-diabetic		Diabetic	
	I	II	III	IV
Number of cases	1	5	3	5
Per cent	7.1	35.7	21.4	35.7
Glycosuria, cases	1	1	2	5
Per cent	100	20	66	100
No glycosuria, cases	0	4	1	0
Per cent	0	80	34	0

I Increased tolerance
II Normal tolerance
III Prediabetic curve
IV Diabetic curve

stop at this point one would be tempted to say that the patient had been cured of diabetes. I followed him through with a series of glucose tolerance tests for the next four years, and the chart shows the fluctuations of these curves with a normal tolerance curve finally in 1929. Whether these fluctuations are expressions of a periodic hyperactivity of the pituitary as suggested by Cushing I am not in a position to say. Many authors call attention to such fluctuations or remissions of the diabetic state in acromegalic patients. (Table IV).

My impression is that while the mechanism of this type of diabetes is different from that of ordinary diabetes, the treatment remains the same, unless there be surgical intervention or irradiation of the pituitary. If the diabetes is not treated, such patients die in coma, just as any other diabetic patient does. (Table III). There are occasional cures reported, but to be sure of this point, it is necessary to make repeated observations over a period of years.

In *Simmonds' disease* in which there is failure of the anterior pituitary, normal blood sugar and an increased glucose tolerance are the usual findings. Wilder has reported two cases both of which showed clinical signs and symptoms of hypophyseal disease. In both cases there were spontaneous attacks of hypoglycemia.

Boschi reported the results of X-ray treatment of the pituitary in a woman who apparently had severe diabetes. Following the irradiation she ceased to excrete any sugar. I also saw a similar case (Chart 2, second case), but it must be noted that the blood sugar was at a normal level before the irradiation treatments were administered.

Lucke has reported that hypophyseal dwarfs are very sensitive to insulin.

In a series of 106 cases of hypopituitary disease I found a non-diabetic type of curve in 67.9 per cent and a diabetic curve in only 32.1 per cent. (Table V).

Kraus of the Prague Medical School noticed in 1923 that at autopsy, diabetic patients showed hypophyses smaller than normal. The eosinophilic cells were diminished and showed retrogressive changes in the cell nuclei. He followed this observation with experimental work and extirpated the pancreas in cats, thereby producing similar changes in the pituitary.

Muthman has reported the work of Eaves who found morphological changes in the anterior lobe of the pituitary which suggested a hyperactivity of the gland following the administration of insulin to a rabbit.

Houssay and Biasotti have shown that in hypophysectomized dogs and other species the removal of the pancreas was not followed by glycosuria. The administration of sugar, however, caused excretion of part of the sugar and an increase in the respiratory quotient. The implantation of the pituitary in these same animals produced diabetes. Davis also ascertained that bilateral hypothalamic lesions followed by pancreatectomy do not produce hyperglycemia and glycosuria.

Anselmino and Hoffman feel that they have proved basically that diabetes mellitus in the human being is occasioned by a disturbance of the pituitary regulating mechanism. As to the mechanism of the action of the pancreatropic substance derived from the anterior lobe of the pituitary, Hoffman and Anselmino reported on a number of insulin-like effects on metabolism which were lacking in dogs without a pancreas. They concluded that the effects on metabolism are to be attributed to an increase in secretion of insulin under the influence of the pancreatropic substance of the anterior lobe of the hypophysis.

Cowley has suggested that in hypophysectomized animals these effects may be due to the unopposed action of insulin.

The diabetogenic substance, according to Collip, can be studied to best advantage in the Houssay dog, that is, in the depancreatized-hypophysectomized animal which becomes, according to Barnes and Regan, very sensitive to insulin and can have hypoglycemic convulsions during fast. When the blood from such an hypophysectomized dog is injected into rabbits it causes a fall in the level of the blood sugar. The hypophysectomized-depancreatized animal shows no glycosuria but often an injection of the pituitary extract produces glycosuria and hyperglycemia. Pituitrin does not produce glycosuria but the injection of whole gland extract will produce it. The acid extract of the anterior lobe, however, produces much more pronounced and persistent glycosuria. When the thyroid is removed, some of the dogs do not show glycosuria under these circumstances.

Weed, Cushing and Jacobson, upon stimulating the superior cervical sympathetic ganglion in animals produced glycosuria. They reasoned that this was effected by the liberation of the hormone through impulses which reached

TABLE III

Death in coma in diabetes accompanying acromegaly

Author	Number of Cases	Reference
Borchardt	Several	*Deutsch. med. Wchnschr.*, 34:946, 1908
Ellis	1	*Lancet*, 1:1200, 1924
Anders and Jameson	1	*Am. J. Med. Sci.*, 148:323, 1914
John	1	*Arch. Int. Med.*, 37:489, 1926
Koopman	Several	*Nederlandsch. Tijdschr. v. Geneesk.*, 2:1071, 1919
Gray	1	*J. Path. and Bact.* Edinburgh, 32:71, 1929
Hunnicutt and Rayle	1	*Ga. Med. Assn. J.*, 15:115, 1926

the hypophysis. They concluded that it is likely that the carbohydrate hormone comes from the chromophilic cells.

Cope and Marks removed the pituitary in animals and the adrenals responded normally to insulin hypoglycemia by liberating epinephrin into the blood stream, but the

epinephrin failed to restore the blood sugar to a normal level in spite of ample reserves of liver glycogen. The hyperglycemic response to injected epinephrin was likewise diminished. Reverse changes were noted, namely resistance to insulin and an increased response to epinephrin when extracts of the anterior lobe of the pituitary were administered. They feel that the anterior lobe of the hypophysis contains a principle which renders the glycogen stores of the liver and possibly those of the muscles susceptible to the mobilizing action of epinephrin. The changes following removal of the hypophysis can not be reversed by the administration of thyroid and hence they are not due to the concurrent thyroid degeneration. The changes produced by the injection of anterior pituitary extract are not prevented by the removal of the thyroid.

Lucke and Hahndel, who studied the mechanism of the action of the contra-insular hormone of the anterior lobe of the pituitary came to the conclusion that its point of attack is in the central nervous system and that the activity of the adrenal system is guided by the hormone from the central system by way of the sympathetic nerve pathway. The mechanism of action corresponds in principle to that observed in a condition of diabetes produced by puncture.

Dogs without their suprarenals are very sensitive to insulin even in states of normal glycemia. The level

TABLE IV

Remissions in diabetes with acromegaly

Author	Reference	Remarks
Bayard (1923)	Chap. and Mod. Pract. London, 1923-24, 1923	Died, pregnancy
[illegible]	Journ. Endoc. & Neurol., 1926, 1927	Died, sugar-free
[illegible]	Die Zuckerkrankheit, Berlin, 1926	2 cases
[illegible]	Lancet, 1923, 1924	Hypophysectomy
[illegible]	Endocrinology	3 cases
[illegible]	Medicine, 6:1, 1927	1 case
[illegible]	Surgery, Boston, 1928	

of the blood sugar does not rise after the injection of the contra-insular hormone in dogs without adrenals. This shows that the adrenals must be involved in the action of the contra-insular hormone of the anterior lobe of the pituitary. Regarding the exact mechanism of action, there are two possibilities: Either the contra-insular hormone formed in the anterior lobe acts directly on the adrenals from the blood system, or through the central nervous system, and the stimulus is relayed to the adrenals by way of the sympathetic nerve tract, thus setting up conditions analogous to the mechanism of action in puncture diabetes.

Animals with denervated adrenals are sensitive to insulin and display an intense increase in the level of blood sugar after the injection of epinephrin. The required hormone equilibrium for the normal maintenance of carbohydrate metabolism in the face of distorted island function of the pancreas can only be effected by the influence of the anterior lobe of the pituitary and by an intact suprarenal pathway.

THE THYROID GLAND

Hyperthyroidism is one clinical condition in which I have had the opportunity to make rather thorough studies of carbohydrate metabolism. The clinical data from my own series and others reported in the literature are now large enough to make some statistical analysis. These show a greater incidence of diabetes in hyperthyroidism than the average, namely 2.31 per cent, in a series of 20,325 cases which I collected in 1932. This is not a huge incidence, but still it is about twice that of diabetes generally. The problem which confronts the clinician is to determine the factors involved and to decide whether any safeguards can be provided to prevent this increased incidence of diabetes in hyperthyroidism.

We know that in hyperthyroidism the liver function is deranged. The liver is poor in glycogen and can not fix glycogen normally. This would be sufficient explanation for the non-physiologic hyperglycemia, but it does not explain the development of diabetes in these patients. Can it be that these patients, because of increased metabolism, consume enormous quantities of food and especially of carbohydrate, and hence place an extra load on the insulogenic function, which may thereby become exhausted, especially if there has been some preexisting "diabetic anlage"? This may be one logical explanation. We know that it is not merely the increased metabolism which is responsible for the hyperglycemia, for if it were, hyperglycemia would be present in the majority of severe cases of hyperthyroidism. Yet this is not the case. Furthermore, were the hyperthyroidism alone responsible for the disturbance in carbohydrate metabolism then certainly such a disturbance would run parallel with the severity of the hyperthyroidism, which also does not conform with the findings. The increase in basal rate, too, bears no relation to the degree of hyperglycemia. Often the mildest thyrotoxicosis produces the most profound dysfunction of carbohydrate metabolism, and on the other hand, the patients with the highest level of blood sugar may respond most promptly and permanently to treatment and often are completely cured. This proves that there are adequate safety factors in the human body.

However, it is impossible to determine beforehand which of these disturbances during hyperthyroidism will right themselves and which will develop into instances of permanent diabetes. In some cases in which there is but slight indication of disturbed carbohydrate metabolism the condition is apparently corrected after thyroidectomy, with no evidence of abnormality for a year or more, and yet later these patients may become severe diabetics. Chart 1 shows such a case.

This patient was a young woman, twenty-six years of age, with severe hyperthyroidism. Her basal metabolic rate was plus 57 per cent. The only thing which led to the investigation of the carbohydrate metabolism was glycosuria which she had on successive days along with normal levels of blood sugar. The glucose tolerance test showed a diabetic curve, and still the daily fasting blood sugar level after this was normal for over a month. Two months after thyroidectomy the glucose tolerance test was repeated and it still showed an abnormal curve. Two more fasting blood sugar determinations three months later were normal. The third glucose tolerance test, seven months after thyroidectomy, showed some improvement, but still gave a prediabetic curve. However, the blood sugar was normal, morning and noon, on the following day.

I did not see the patient again until recently when she was sent to me because she had diabetes which her physician could not control. Her subsequent story is shown on the chart. She has severe diabetes now, five years after

the thyroidectomy, and this condition evolved from the mildest sort of carbohydrate disturbance during hyperthyroidism.

It brings out the point that clinically we can not afford to disregard deviations in carbohydrate metabolism during hyperthyroidism. Similar and more dramatic stories I could present by the score.

It was known almost a century ago that persons and animals with endemic goiter develop hypertrophy of the anterior lobe of the pituitary gland. Thyroid enlargement and hyperactivity with acromegaly have long been noted. It has also been known for a long time that the thyroid acts as a depressant of the insulogenic function. Only recently, has it been demonstrated that the administration of desiccated thyroid prevents this pituitary effect and furthermore that the acidophilic granules of the anterior lobe produce a thyroid-stimulating principle, which causes hypertrophy of the epithelial cells of the thyroid vesicles with an increase in thyroid secretion.

Shockaert has induced enormous hypertrophy of the duck's thyroid accompanied by exophthalmos by the injection of extracts of the anterior lobe of the pituitary. Experimental exophthalmos can be produced readily by injections of pituitary extract into thyroidectomized animals. Houssay has carried out experiments with dogs which clearly indicate that the pituitary influence controls the thyroid in these animals.

TABLE V

Glucose tolerance curves in hypopituitarism (John).

Type of Curve	Non-diabetic		Diabetic	
	I	II	III	IV
Number of cases	36	36	27	7
Per cent	33.9	33.9	25.5	6.6
Glycosuria, cases	6	15	13	7
Per cent	16.6	41	49.6	100
No glycosuria, cases	30	21	14	0
Per cent	83.4	59	50.4	0

Since the thyrotropic hormone causes an increased activity of the thyroid gland which in turn increases the metabolism, we can rightfully expect an increased demand on the insulogenic function. The secretion of insulin keeps pace with this demand so long as the pancreas is intact, but if it is not, there is evidence of insulin deficiency, which manifests itself as a non-physiologic hyperglycemia. Another explanation for non-physiologic hyperglycemia in hyperthyroidism would be a direct neutralization or depression of the insulin action by the excess thyroid secretion.

There is still another possible explanation for hyperglycemia in hyperthyroidism. We know that certain infections produce diabetes and that already existent diabetes is much aggravated by an infection. The toxemia with its accompanying acidosis probably is the damaging factor. In the normal person, the level of aceto-acetic acid never exceeds 3.5 mg. per cent and that of beta-oxybutyric acid, 5.5 mg. per cent. In the thyrotoxic patient, these values are high, 16 mg. per cent for aceto-acetic acid, and 18 mg. per cent for the beta-oxybutyric acid. Hence the toxemia of hyperthyroidism might account for the damage to the islands.

The degree of liver derangement probably goes hand in hand with the severity and duration of the hyperthyroidism, and yet there is no consistent change in the glucose tolerance curve to correspond to this.

The thyroid is regarded as a depressant of insulogenic function, and yet it is likely that this is not due to the direct effect of the thyroxin on the islands of Langerhans, but reversely, to the direct effect of insulin on the thyroid. Both hormones exert their effect on the liver, muscles and the carbohydrate metabolism, partly supporting each other, partly increasing the common utilization of these hormones. If one or another part of this synergistic whole is out of balance, this would explain why in some cases of hyperthyroidism there is an increased utilization of sugar, and in others a decreased utilization.

I feel more and more that when diabetes develops in a patient with hyperthyroidism, a diminished insulogenic reserve must have been present beforehand.

THE SUPRARENAL GLANDS

The relationship of the suprarenal glands to carbohydrate metabolism has been known for a long time. Clinically, in Addison's disease, the blood sugar level usually is low, and in suprarenal tumors in which there is an excess of adrenal secretion, the blood sugar level often is increased.

An increased quantity of insulin in the blood stream seems to release more epinephrin (Kugelmann). Excessive output of insulin induces enlargement of the cortex (Hartman). Animals without the suprarenals are much more sensitive to insulin than normal animals. Experimental diabetes is much less marked in the presence of adrenal insufficiency than in normal animals. This is due at least in part to the absence of the cortical hormone (Hartman and Brownell). In suprarenal insufficiency the glycogen is slowly regenerated after severe fatigue (Dambrost). In late stages of insufficiency the liver and muscle glycogen are much depleted and the blood sugar usually falls.

In 1901 the discovery by Blum that the injection of epinephrin was followed by hyperglycemia and glycosuria, gave rise to the theory that this substance was the physiologic antagonist of insulin. That same year Zuelzer demonstrated in a rabbit that the blood sugar level rises as high as 700 mg. per cent and higher. Dogon in 1904 found that the glycogen in the liver is decreased so that after a larger dose of epinephrin the liver can become glycogen-free. Velich, Blum and others found that the intensity of the adrenalin hyperglycemia and glycosuria depends on the glycogen quantity of the liver. If the liver is made glycogen-free the blood sugar will not rise after adrenalin injection. It was Velich who first proved that the adrenalin glycosuria is not caused by pancreatic insufficiency. The Vienna school built up an elaborate theory of glandular interrelationships between the thyroid, adrenal medulla and the pancreas to explain the effects of pancreatectomy. This view has come to be known as the "overproduction theory." The main thesis is that the diabetic condition is not entirely brought about by a failure to metabolize glucose, but rather by an overproduction of this substance from protein and fat. On the basis of the glycosuric action of epinephrin, they argued that the uncompensated action of the adrenal medulla in the absence of the pancreas brought about this overproduction. In brief, according to this theory, diabetes mellitus was in reality hyperadrenalism (Long).

The work of many investigators has exposed the false-

ness of this view. In the first place, epinephrin, although producing glycosuria and depletion of liver glycogen, does not stimulate protein metabolism nor does it produce the degree of ketonuria that is present in diabetes. Nor does its continued injection produce a persistent glycosuria such as is seen in the fasting animal. The more recent work of Cori has demonstrated that epinephrin, although at first reducing liver glycogen, finally brings about a marked increase in this substance at the expense of the muscle glycogen. It would appear at the present time that the effects of epinephrin are limited to the formed carbohydrate elements in the body and that it is incapable of stimulating the production of glucose from protein.

In hypophysectomized animals the suprarenals show an atrophy which is limited to the inner layers of the cortex; the medulla remains intact (Long). Barnes and his coworkers in their studies upon the effects of suppression of epinephrin secretion upon pancreatic diabetes in dogs found that such a procedure may produce some amelioration of the diabetes, but this effect is inconsistant. Of greater interest is their finding that the insulin required to maintain such animals is often only a fifth or a quarter of the quantity required when the adrenal medulla is active. If epinephrin is infused at a physiologic rate into such animals the insulin requirement promptly returns to normal.

DeTakats and his associates have shown that section of the splanchnic nerves, coeliac ganglionectomy or denervation of the suprarenals results in a decreased insulin requirement both in dogs and in human diabetics. In interpreting these experiments it should be remembered that epinephrin does not alter the nitrogen metabolism and there is a good reason for believing that its effects are limited to the formed carbohydrate stores of the body (Long).

Britton, Zwemer and others have shown that the marked hypoglycemia and low liver glycogen stores of adrenalectomized cats are relieved by the injection of cortical extracts that will maintain such animals in good health.

Long and his associates removed the suprarenals and the pancreas in cats; these animals were injected daily with cordical extract, but no insulin was administered. The effect of total suprarenalectomy upon pancreatic diabetes they found was strikingly similar to that of hypophysectomy. Hyperglycemia and glycosuria were much reduced; nitrogen excretion and the D/N ratio were decreased; ketonuria was very slight and acidosis did not develop; the survival period of the animals was much increased; hypoglycemia was common. There was occasionally some improvement of carbohydrate tolerance but this was not so marked as in the Houssay dogs. In another series of experiments they have shown that it is the adrenal cortex and not the medulla that is responsible for these changes, since animals from which the adrenal medulla is removed rapidly die of diabetes after pancreatectomy. These authors suggested that the hypophysis controls sugar formation from protein through the adrenal cortex. This they say is tantamount to saying that the adrenal cortex contains a diabetogenic substance or a contra-insulin hormone.

LIVER

Claude Bernard originally considered glucose as an internal secretion of the liver, differentiating it from bile, the external secretion of the liver. From this ingenious observation there arose a whole series of teachings about internal secretions which in time eliminated from consideration that very first representative, glucose. More intensive study and increased knowledge of metabolism, however, showed that Claude Bernard's definition had a healthy kernel, even though the sense today differs from that understood by its author.

The regulation of the blood sugar level is not a simple, but a complex affair. Hyperglycemia *per se* stimulates the pancreas to production of insulin for its control. Hypoglycemia, on the other hand, stimulates the secretion of epinephrin which releases glucose from the liver to counteract the hypoglycemia. The Kupfer cells in the liver also play no small part in the regulatory mechanism of carbohydrate metabolism and the blood sugar level, as shown recently by Althausen and his associates. The secretion of insulin is regulated by means of a nervous mechanism and also through a humoral mechanism. Both regulatory mechanisms are activated by the glucose itself, even in small concentrations and thereby its action can be considered purely hormonal. The suprarenal factor depends on the blood sugar level, which, if lowered below a certain point, calls forth an increased production of epinephrin from the medulla, but this occurs only if the splanchnic nerves are intact. If these nerves are severed or if their function is prevented by ergotamin, such a reaction does not take place. The transfusion of hypoglycemic blood, activating the nerve centers dealing with the blood sugar regulation also calls forth adrenal secretion only if the innervation of this gland is intact.

It is also possible that the changes in the level of glucose give rise even in the tissues themselves to a regulatory mechanism. In this manner certain finer differences in the concentration are regulated which, however, are insufficient to cause marked stimulation of the larger mechanisms. Charvat and Gjuric in their studies of the relationship of the arteriovenous differences of blood sugar in normal persons, diabetics, and patients with hyperthyroidism, found upon injection of normal saline that when the tissues have a marked avidity for sugar, such as in hyperthyroidism, a slight stimulation with very small quantities of sugar in the arterial circulation is enough to cause almost immediately its fixation and finally even its oxidation, so that the level in the venous blood is lowered. This occurs much earlier than the reflex stimulation of insulin secretion which, as Pollack first showed, takes place about a half hour after the ingestion of glucose.

In all cases glucose acts directly or indirectly as a regulator and for that reason the liver is classed in the endocrine system as an organ maintaining hormonally the standard circulation of glucose, a substance necessary to life. Furthermore, glucose has a typical hormonal function in that, according to its concentration, it produces varying effects, which is true of other hormones. It is also known that glucose is a mighty protector of the liver cell, as Mann, Bollman and others have shown.

Another function of the liver which is closely connected with the glycoregulatory problem, is the production of glykaemin. Glykaemin is a special hormone which dializes through a living membrane, is soluble in alcohol and causes a rise in blood sugar through the prevention of the fixing ability of the sugar in the tissue and liver cells. This in turn increases the sugar output of the liver and hyperglycemia results. It was through the clever work of O. Loewi and his pupils, Hasenöhrl, Depisch, Ueberrack, Högler and Thomann that it was demonstrated that the diabetic glycoregulatory derangement is caused by the primary inability of liver cells to fix the circulating sugar. In their study of the reasons for this, they found that it

was not the inadequacy of insulin in itself, but the presence of some special substance which prevented the cells from fixing the sugar. In this case it was the red corpuscles. This substance, glykaemin, is a direct antagonist of insulin, and is manufactured under certain conditions by the liver. It can be washed out by means of adrenalin from the liver, it is present after the sympathetic stimulation of the liver, it is found after a heavy carbohydrate diet. Its production is depressed by insulin and it is found in the blood stream after extirpation of the pancreas. Under certain conditions it is produced by insulin hypoglycemia, probably through some interaction of the suprarenals, in which case it appears as a compensatory mechanism (Högler, Thomann and Ueberrack). It is formed in the liver and can be found in the hepatic vein, after adequate stimulation, earlier than in the rest of the circulation.

Normally it is present in very small quantities in the blood stream and its effect is disguised by insulin. If sugar is administered orally, the glykaemin output as well as the insulin output is increased. In the normal individual insulin soon dominates. If the innervation of the pancreas is interrupted either by atropin or vagotomy the effect of glykaemin can be

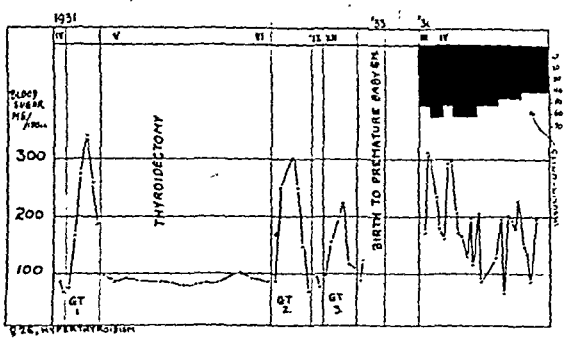


Chart 1. Blood sugar studies in a case of hyperthyroidism showing glycosuria and a slight carbohydrate metabolism during the hyperactive stage which cleared up following thyroidectomy only to reappear five years later as severe diabetes.

seen after a glucose meal. In the fasting state, the effect of glykaemin can not be noted because the pancreas can adequately counteract it and control it.

Minkowski and Allen have shown that if one-tenth of the pancreas is left in the animal, diabetes is not produced and Pollak has stated that in man if the insular apparatus is reduced by one-half, severe diabetes supervenes. Loewi explains this difference by the fact that in human diabetes there is primarily some sort of liver damage which leads to an increased secretion of glykaemin. Because of this, the pancreas is kept at a constant level of compensatory hyperfunction and thus finally becomes exhausted.

The internal secretion of the pancreas is necessary for the proper functioning of the liver. Following the extirpation of the pancreas, the liver not only loses all its glycogen, but undergoes fatty degeneration and functional deterioration.

These problems are very complex and the only thing I wish to show is how closely the liver is connected with the hormonal function of the pancreas. On the other hand, without the liver, the islands of the pancreas lose their "raison d'etre" for even though the insulin then can function in the periphery in the fixation of the sugar in the tissues, it can not increase the oxidation of the sugar in the body, which is necessary to maintain one of the basic functions of life. Through this hepatopancreatic correlation, the liver is entrenched firmly in the endocrine family.

THE SALIVARY GLANDS

Many clinical observations and considerable experimental work has been done in the past decade in an effort to learn the true function and significance of the salivary glands. In spite of the tremendous amount of work that has been done on this problem, the question as to whether or not the salivary glands have an internal secretion has not yet been answered satisfactorily. Considerable clinical and experimental evidence has accrued to indicate that there probably is an indirect, if not a direct relationship between the salivary glands and various glands of internal secretion (Charvat, Bauer, Römer).

In 1897 Ferrannini reported a case of salivary diabetes, in which glycosuria alternated with and replaced the glycosialorrhea. This case suggested a possible reciprocal relationship between the salivary glands and the pancreas. On the basis of experiments with extracts of the salivary glands, Farroni, who was Ferrannini's assistant, postulated an endocrine action of the salivary glands analogous to that of the pancreas.

A decade later, Best, Scott and Banting found much insulin in the salivary glands, which they thought was due to extravasation from the blood stream. Glaser and Bannet analyzed chemically a few kilograms of salivary glands and did not find insulin but demonstrated the presence of peroxydases and oxydases, which might replace the secretion of the pancreas in some cases.

Utimura found that after parotidectomy the action of the thyroid was increased, the islands of Langerhans were enlarged, and there was an increase in the amount of liver glycogen. When the submaxillary glands were removed, these changes were reversed, and if both parotids and the submaxillary glands were extirpated there were no changes in the pancreas and the liver.

Mansfeld and Schmidt ligated the parotid glands of dogs, and found that the level of the blood sugar was lowered. Later, the ligated glands were extirpated and the level of dextrose returned to normal. In dogs with experimental diabetes, produced by partial removal of the pancreas, ligation of the parotid ducts controlled the hyperglycemia. However, ligation of the ducts of Steno had no effect in controlling the diabetes produced by total removal of the pancreas. Mansfeld concluded from these observations that the parotid glands must produce a substance which stimulates the pancreas to increased function. Seelig and also Dobrzaniecki and Michalowski repeated Mansfeld's experiments and confirmed his observations.

In 1932 Zimmermann made similar studies and also made extensive histologic studies of the parotid glands removed at varying intervals after ligation. Goljanitsky also made comparative histologic studies of the pancreas and the parotid. He felt that the internal secretion of the salivary gland has a function similar to that of insulin and that both hormones are antagonistic to epinephrin.

As a result of these experiments on animals, numerous attempts, (Goljanitsky, Seelig) have been made to treat diabetic patients by ligation of the parotid ducts, but the results have not been sufficiently encouraging to warrant any wide application of the method.

Parotid swelling during mumps accompanied by a tenderness in the pancreas is not a rare finding. The development of diabetes following epidemic parotitis too is

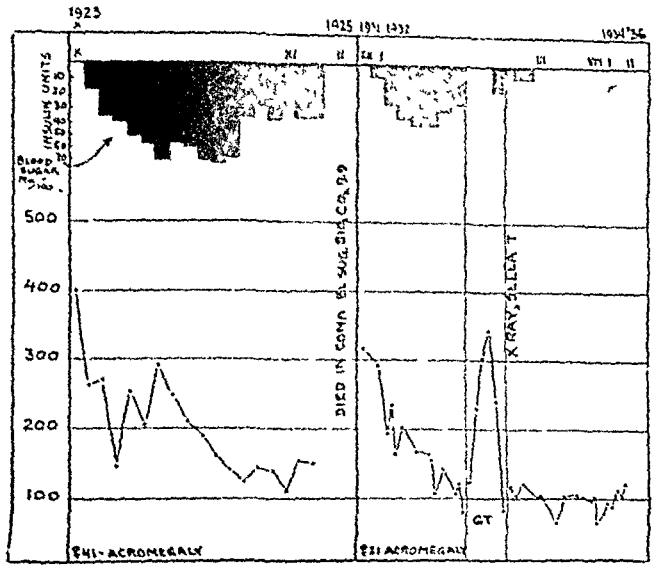


Chart 2. Two cases of acromegaly with observations on the blood sugar in each. One died in coma, the other cleared up and stays cleared up on normal diet.

not uncommon. The cases in children that I reviewed in 1934 from among my own series and those gathered from the literature totaled twenty-eight. In these cases it is difficult to say whether the damage was primarily in the pancreas or whether impairment of parotid function had some bearing.

In 1932 Charvat reported three cases of mild diabetes in which there was also a symmetrical painless non-inflammatory swelling of the parotid glands, which had persisted from six months to three years. He felt that the parotid swelling represented a compensatory hyperplasia of the glandular parenchyma in response to failing insulogenic function or a symptom of endocrine hyperfunction of the salivary glands, which might account also for the mildness of the diabetic state. In two of these patients, the parotid swelling decreased with treatment for the diabetes.

Flamm became interested in the study of hypertrophy of the parotid glands as a symptom of diabetes through observing a woman with hypertension who had frequent attacks of swelling of the salivary glands, which were not accompanied by pain, fever or other signs of inflammation. In the intervals between attacks, the parotid glands remained somewhat larger than normal. Later diabetes was discovered with continued recurrence of parotid hypertrophy. This caused a peculiar transformation of the features of the face, which Flamm noticed was quite characteristic of a good many patients with diabetes.

In a group of twenty-seven patients with swelling of the parotid glands, sixteen showed glycosuria and also an increase in the fasting blood sugar. Dextrose tolerance tests showed some decreased tolerance in the other eleven patients. He also noted that most of these patients belonged to the constitutional type designated as asthenic hypertension diabetes. Flamm offered no direct explanation of the functional processes underlying this hypertrophy of the parotids in diabetic patients, but concluded that it might be interpreted as a compensatory process.

In 1933, I published observations on four patients with enlargement of the parotid glands and mild diabetes. Recently I have seen another case of this type. None of these patients sought medical advice because of the diabetic condition, although in one case diabetes had been diagnosed previously but the patient had not had adequate or systematic treatment. In each instance the enlargement of the parotid glands was noted on the clinical examination with subsequent detection of glycosuria and hyperglycemia. In none of these cases could the parotid hypertrophy be attributed to any inflammatory or infectious process. All five patients were obese and there was a striking similarity in their facial appearance. The diabetes was mild in all these cases and was easily controlled with moderate dietary restriction and small doses of insulin. Whether the parotid swelling represents a compensatory process brought about by a decreased pancreatic function, as Charvat and Flamm have suggested, remains an open question. At present I feel that this problem is largely of academic interest until such time as the internal secretion of the parotid can be isolated and its function determined.

THE PARATHYROID GLANDS

There is but little evidence of any direct association between the function of the pancreas and of the parathyroids, although temporary glycosuria of the alimentary type has been reported in cases of idiopathic tetany. However in tetany the carbohydrate metabolism does not manifest the same disturbance in all cases. Charvat says that at times he has found very low glucose tolerance curves, and at other times the glycemia is pronounced, and in one case he found glycosuria. The variation is probably because there is rarely a disturbance of a single gland, and these bizarre findings are for the most part the result of pluriglandular dysfunction.

Despite these inconclusive clinical findings, we do know that there is a definite and important relationship between carbohydrate metabolism and phosphate metabolism. Retention of phosphates is an outstanding metabolic feature in parathyroprival tetany. In parathyroid insufficiency the blood phosphates are increased and the urinary phosphates are decreased, as shown by McCullagh. In 1932 I reported a study of phosphate curves made along with blood sugar curves during glucose tolerance tests. When the sugar curve increased, the phosphate curve decreased, and vice versa. Harrop and Benedict, who reported similar studies, believe that phosphates are utilized temporarily during the transference of glucose from the blood.

Experimentally in tetany or parathyroid insuffi-

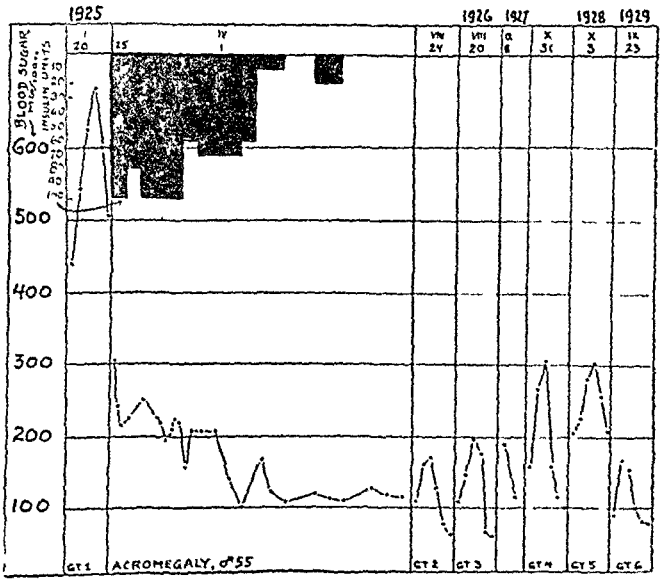


Chart 3. Blood sugar studies on a case of acromegaly, who shows periodic recessions of his diabetic condition.

ciency there seems to be insufficient fixation of sugar in the liver and in other instances there is a glycoregulatory disturbance. Houssay and Biasotti report marked degenerative changes in the parathyroids in the hypophysectomized, pancreatectomized animals. A dependence of the parathyroids upon the anterior pituitary seems rather clear in some species (Hertz, Houssay) but the evidence for a specific pituitary hormone with a direct action on the parathyroids is relatively scanty.

THE GONADS

That the sexual function is influenced by and also exerts an effect on carbohydrate metabolism is well known clinically. The relief of diabetes in many cases following the climacteric has been observed by every specialist in the field. The failure of menstruation and of all reproductive function in cases of severe diabetes not controlled by insulin is also a matter of common knowledge. The lowered glucose tolerance in many pregnant women has also been observed frequently. In some of these instances, the disturbance is corrected after delivery, and in others, frank diabetes may supervene. It is difficult to say whether in these cases the patient had a decreased insulogenic reserve to start with, or whether other factors are responsible.

The actual incidence of diabetes in the eighth and ninth decades is comparatively rare. According to Eiselt such patients are insulin resistant. Arteriosclerosis is a common finding in this group and pathologically there are interlobular and intralobular changes in the pancreas along with atrophy and sclerosis of the islands of Langerhans, according to Weischselbaum. Just what endocrine changes, especially gonadal changes, play a part here is very difficult to state, because there is probably a general subnormal function of all these organs.

It is well known that the withdrawal of the ovarian or testicular hormone causes marked changes in the anterior lobe of the pituitary, and it is probably through the influence of this disturbed pituitary function that other bodily changes occur. No very conclusive studies of the carbohydrate metabolism in eunuchs has been made, and so the effect on the pancreas of the withdrawal of the sexual hormones is extremely difficult to determine.

There are evidences, however, that the insulogenic function is somewhat disturbed. Charvat has reported lowered glucose tolerance curves in eunuchs. However, in obese eunuchs he found that the glucose tolerance was increased. A small group of glucose tolerance tests which I made on castrates showed invariably either a normal or an increased tolerance. This, however, does not prove anything, for to judge and to evaluate such cases would require a large series, and what is more important, a controlled series. Glucose tolerance tests should be done before castration and then followed with repeated tests each year or so following gonadectomy. Such data I have not been able to find in the literature.

(An extensive bibliography had to be omitted for lack of space—Editor).

Blood Pressure Changes During Defecation

By

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DURING the year 1931 in the course of my practice I attended six patients who expired suddenly from cerebral hemorrhage. Death occurred in these patients while they were on the toilet seat attempting to move their bowels. All of these patients had been affected with hypertension and constipation. The conclusion seemed likely that there must exist some relationship between these deaths and hypertension associated with constipation.

A consideration of this relationship suggested the questions: (1) during the act of defecation does a rise in blood pressure occur? (2) what is the average rise, if such a rise does occur? (3) is there a relationship between the blood pressure and the degree of straining? (4) can the change in blood pressure be sufficient possibly to threaten rupture of a blood vessel wall? (5) during defecation are different diseases associated with specific blood pressure changes?

In view of the fact that a search of the literature disclosed no answers to these questions, since 1931 I have examined over 300 male patients. I have measured blood pressures in the usual manner. These blood

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TABLE I

Type of Patient	No. of Patients Examined	Average Age	Average B.P. Before Defecation	Average Increase in B.P. During Defecation	Highest B.P. Increase After Maximal Stress
Normal B. P.	90	38	115 70	20 15	110 80
Hypertension	70	60	160 95	25 15	100 70
Obese, 15 or more lbs. overweight	40	50	125 85	15 10	70 40
Underweight, 10 or more lbs.	25	45	120 75	25 20	90 70
Chronic Myocarditis Not Decompensated	20	62	130 85	20 15	60 20
Asthma	15	35	120 75	15 10	40 30
Hyperthyroid	10	29	135 70	15 15	70 60
Angina Pectoris	10	57	125 85	20 10	60 30
Diabetes	10	45	120 85	20 15	100 70
Chronic Pulmonary T.B.	8	34	110 65	20 10	40 40
Hypothyroid	5	35	110 70	20 15	80 60

pressures were recorded while the patient was sitting on a toilet seat engaged in moving his bowels. The results are summarized in Table I.

COMMENT

Table I shows a significant rise in blood pressure during defecation. With a corresponding degree of stress, this rise averaged 20/15. But the greater the degree of stress, the higher the rise in blood pressure. In one patient this effort produced an increase amounting to 110/88. Certainly an increase in blood pressure such as this would appear to add considerably towards the danger of rupture of a diseased blood vessel wall.

Examination of patients affected with different diseases as shown in the Table revealed nothing specific, the blood pressure changes not differing markedly from the average. Alterations of blood pressure in disease seemed different only in so far as the disease interfered with the ability to strain.

CONCLUSION

The act of defecation is attended by an increase in blood pressure. This increase in blood pressure is greater according as the straining at stool is greater.

Etiology of Gall Stones:

II. *The Relationship of the pH of Bile to the Formation and the Dissolution of Gall Stones**

By

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and

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WHILE pursuing experimental studies on the etiology of gall stones, it became apparent that a change in the pH of bile was one of the most important factors in the formation of stones. A survey of the literature reveals but little data regarding the pH of bile in animals or human subjects. Most of the available data are concerned with the pH of dog's bile. In a previous study, the authors (1) as well as others, noted that human stones placed in a dog's gall bladder would dissolve. The explanation of this observation will be considered below. On the basis of this finding in the dog, a study of the pH of bile in other animals was made. Nichols (2) observed that the bile of guinea pigs is alkaline to litmus but the pH was not determined by the electrometric method, since this method was not available at that time. In a recent communication (1), the normal pH of guinea pig's bile was stated to average 8.89 in 26 specimens. Since this report we have examined 45 specimens and found the hydrogen-ion concentration to range from 8.66 to 9.14 with an average pH of 8.93. The hydrogen-ion concentration in our studies was determined electro-

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metrically, using the Wilson type hydrogen electrode (3) at 25° ± 0.5° C.

Since it is now well established that human gall stones will dissolve in the normal gall bladder of dogs and inasmuch as it is our impression that a change in the pH of bile is an important factor in this dissolution, further proof of the effect of pH upon stones suggested itself. This information might aid not only in the understanding of this dissolution but might also reveal the mechanism of the formation of stones.

TABLE I
Controls

pH	Weight of Stone Grams Before	pH	Weight of Stone Grams After	Number of days after implantation of stone in gall bladder
8.88	0.044	8.80	0.043	110
8.70	0.034	8.56	0.028	114
8.90	0.045		0.044	112
9.07	0.038	9.00	0.035	112
8.72	0.019		0.019	121
8.92	0.039	8.88	0.039	112
8.85	0.038	8.80	0.032	114

EXPERIMENTAL

Human gall stones of the cholesterol type were placed in the alkaline bile of seven guinea pigs; the results obtained are tabulated in Table I. The pH determinations were made on bile obtained by needle puncture prior to opening the gall bladder and each stone, after drying to a constant weight, was weighed and placed in the gall bladder. This table indicates quite strikingly that gall stones are not affected by the guinea pig's alkaline bile even after a long period of time. It also demonstrates that practically no change occurs in the pH of the bile owing to the presence of stones.

This suggests that if one could change the pH of the guinea pig's bile from alkaline to acid by chemical means it might be possible to bring about dissolution of the stones. Seven guinea pigs were therefore given a ten per cent solution of sodium dihydrogen phosphate in large doses. In four, normal control guinea pigs were used and in three, stones were placed in the gall bladders. Table II presents the findings of this experiment. It will be seen that no significant change in the pH or in the weight of the stones took place, indicating that a solution of ten per cent sodium dihydrogen phosphate administered orally had no demonstrable effect upon the pH of the bile.

TABLE II
Phosphate feedings

pH	Weight of Stone Grams Before	Weight of Stone Grams After	Number of Days	Amount Administered c.c.
8.73	0.016	0.016	25	100
8.88	0.019	0.018	25	100
9.07	0.020	0.020	25	100
8.93	No stones		29	145
8.80	No stones		29	145
8.83	No stones		29	145
8.86	No stones		5	45

To seven guinea pigs a four per cent hydroalcoholic solution of salicylic acid was administered orally after stones were placed in the gall bladders, in order to determine whether or not this acid would affect the bile or dissolve stones. Table III presents the data obtained in this experiment. It will be seen that no significant change has occurred in the weight of the stones or in the pH of the bile.

TABLE III
Salicylic acid feeding

pH	Weight of Stone Grams Before	Weight of Stone Grams After	pH	Number of Days	Amount Administered c.c.
	0.029	0.031	9.00	17	71.0
	0.019	0.019		17	71.0
8.91	0.028	0.027		9	26.5
9.06	0.043	0.040	8.90	5	15.0
9.14	0.018	0.016		2	6.0
8.83	0.017	0.017	8.80	9	26.5
9.03	0.032	0.033	9.01	3	6.5

A two per cent hydroalcoholic solution of glycocholic acid (C. P. Riedel de Haen, Inc.) was administered orally to four guinea pigs. This acid was found to be extremely toxic even in small doses so that it could not be given for long periods. Table IV presents the findings in this series. No significant change in the weight of the stones was noted. The pH of the bile following the administration of glycocholic acid was not obtained because insufficient or inspissated bile was present in the gall bladders.

SUMMARY

It has been shown conclusively that the acid bile of the dog's gall bladder will dissolve human cholesterol gall stones. In the present report the effect on human gall stones of an alkaline bile as is normally found in the guinea pig's gall bladder was determined. It occurred to us that since human gall stones dissolved in acid bile it was theoretically unlikely that similar dissolution would occur in alkaline bile. Our experiments have shown that gall stones do not dissolve in the guinea pig's alkaline bile even after a long period of time.

TABLE IV
Glycocholic acid

pH	Weight of Stone Grams Before	Weight of Stone Grams After	Number of Days	Amount Administered c.c.
8.91	0.024	0.020	9	28
8.88	0.053	0.053	5	17
	0.015	0.016	4	13
	0.021	0.022	2	6

The average normal pH of dog's gall bladder bile,

determined by the electrometric method is 6.85 while the average pH of the guinea pig's gall bladder bile is 8.93.

Certain substances, namely, sodium dihydrogen phosphate, salicylic acid and glycocholic acid, known to be eliminated partially by the biliary system, do not upon oral administration, influence the pH of bile. Apparently, the pH of bile, although we are fully cognizant that this is a resultant of other factors, is an important etiologic factor in the dissolution of gall stones.

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Peptic Ulcer in Children: A Follow-up Study of Cases Reported Previously and a Report of Additional Cases*

By

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and

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FOUR years ago in a paper on peptic ulcer in children (1) the authors in conjunction with I. P. Bronstein called attention to the fact that duodenal ulcers in children were relatively frequent occurrences. There were comparatively few reports of this condition in the literature. The reason for the infrequency, it was suggested, was that digestive upsets in children were not always given the attention they merited. Since the appearance of our first paper more than twenty-five additional reports on gastric and duodenal ulcers in children have appeared in print. Foshee (2) collected eighteen cases of gastric ulcer and added one more from his own experience. We have also noted that the diagnosis of peptic ulcer in children is made more frequently where previously a statement of its frequency was looked askance at. We are at this time reporting on the subsequent course of the five roentgenologically proven cases of duodenal ulcer in children previously cited and submitting the records of eight additional cases.

Case 1. B. W., female, age 9½ in 1932, complained of a more or less regularly recurring post-prandial distress for three years. Because of an urticarial rash which occurred coincidentally with vernal and autumnal recrudescenses of her distress, the symptoms were thought to be of allergic origin. However, in spite of some definitely positive responses to skin tests the patient was able to eat the very food she was apparently sensitive to without any ill effects. She now weighs 119½ lbs. and is practically free from distress. Fluoroscopic examinations at six months intervals have repeatedly confirmed the original diagnosis of duodenal ulcer although the lesion is becoming somewhat less readily recognizable.

Case 2. M. Z., female, age 11 in 1932, complained of an irregular post prandial discomfort for six months prior to coming to the clinic. There was a definitely demonstrable duodenal defect on the posterior duodenal wall. She was a professional dancer and did not watch her diet carefully. Reexamination in 1933 again showed the defect. In 1934 she was admitted to the children's division of the Michael Reese Hospital because of severe abdominal pain and placed on an ulcer regime, and became and remained free from distress until January, 1935. In September, 1935, she was operated upon for acute appendicitis and has remained free from distress up to the present time.

Case 3. N. S., male, age 13, was well until five months prior to coming to the clinic, at which time he began to complain of post-prandial distress. Two roentgenologic examinations revealed a duodenal defect. He was placed on ambulatory management and remained free from distress for three years. Because of a slight recurrence of symptoms in June, 1935, he was reexamined and the lesion was again demonstrable. He has been free from distress since then although he swerves from his diet from time to time.

Case 4. F. A., female, age 5, was seen in consultation by one of us in 1931 with Dr. W. J. Corcoran. Her gastro-intestinal complaints appeared one month previously and consisted of pain after eating. She has been lost track of and therefore no subsequent history can be given.

Case 5. The history of G. K., age 8½, dated back to ten weeks after birth when she first vomited a small amount of blood. Hematemesis occurred at intervals until she was three years old. At the age of 6 she again vomited blood and complained of substernal distress on taking food. Hematemesis occurred on and off until one month before we saw her, when a profuse hemorrhage occurred. One month later X-ray examinations failed to reveal a gastro-intestinal lesion which might account for the hemorrhages. Because the bleeding continued and a severe anemia developed, she was sent back to Dr. H. M. Richter, the referring physician, for transfusion and exploration. Two small shallow ulcers were found on the posterior duodenal wall one centimeter from the pylorus, only after an incision was made in the duodenum. Subsequent to the appearance of our report she developed increasing pain on swallowing, requiring at first direct dilatation and then retrograde dilatation with the aid of a string passed into the stomach through a gastrostomy. When the family moved to Philadelphia the child was placed in the care of Dr. Gabriel Tucker who continued the treatment. This child had multiple ulcers of years standing, involving the duodenum and the esophagus, the latter leading to stricture.

PRESENT SERIES

Case 1. J. R., female, age 11, came to the office in 1934 complaining of epigastric pain over a period of six months, coming on one-half hour after taking food and relieved by vomiting or eating. X-ray examination revealed a definite duodenal defect and duodenal stasis. She was completely relieved of her distress on ambulatory management and has remained so up to the present time.

Case 2. R. R., age 12, was first seen in 1932. He had

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had more or less post-prandial discomfort for four years, with occasional freedom from all distress. Soda bicarbonate afforded relief. A gastric analysis revealed 35 free and 58 total acid. X-ray examination demonstrated a typical duodenal defect. He was placed on ambulatory ulcer management and has been free from distress when last heard of in September, 1936. It is interesting to note that at the time the child was being examined the father was being treated for duodenal ulcer also.

Case 3. The history of S. L., male, age 11 in 1932, is that since the age of 8 months he would vomit everything he ate a short time after taking food. At times the vomiting was projectile in character. When his meals were restricted to small quantities he would vomit much less. At the age of three he developed epigastric cramps which were relieved by vomiting. During the last two years he complained of a feeling of a lump in the epigastrium, coming on fifteen minutes after a large meal or when he became hungry at school. Small amounts of bland food relieved the pain. X-ray examination revealed a definite duodenal defect. A regime of a soft comminuted diet, frequent feedings and tincture of belladonna afforded him complete relief of his symptoms. When seen three years later he was free from any distress.

Case 4. A. W., male, age 14, came to the clinic in September, 1934, stating that after eating hamburger steak or a full meal he became nauseated, belched considerably, passed much flatus, and had severe abdominal cramps. One month later he developed pain a few minutes to an hour and a half regularly after taking food.

During this period he was receiving injections of antuitrin-S in another department of the clinic for undescended testicles. X-ray examination revealed a definite duodenal defect. He obtained relief of his distress when he was placed on a diet of frequent feedings of bland comminuted food, and a powder containing fifteen grains each of calcium carbonate and soda bicardonate, and also five minims tincture of belladonna after the morning, noon and evening meals. Again it is interesting to note that 13 years previously his mother had undergone a subtotal gastric resection for duodenal ulcer.

Case 5. J. W., was 21 years old when he first presented himself in the gastro-intestinal clinic. In April, 1927, at the age of thirteen he came to the pediatric clinic stating that for ten days he had pain in the epigastrium and left lower quadrant of the abdomen. The pain appeared one hour after a meal, especially hamburger sausages, became worse after two hours, and so severe that "he was doubled up." This condition recurred in 1928, 1929 and 1933. In 1935 he began to complain of heart burn which was relieved by soda or vomiting. X-ray examination showed fasting retention and a clover leaf deformity of the duodenum. The patient refused to come back to the clinic for treatment or further observation.

Case 6. M. K., age 12, female, came to the clinic on April 3, 1935, complaining of pain in the right upper quadrant of the abdomen for one year. The pain came on two hours after taking food and occasionally awakened her from sleep. She had frequent hunger pains while at school. She had had many sore throats. X-ray examination revealed a definite duodenal defect, and tenderness on pressure over the duodenum. Relief of her symptoms was obtained on ambulatory ulcer management.

Case 7. E. M., age 12, male, came to the clinic in November, 1934, stating that for two years he had periumbilical pain after eating. The pain persisted for several hours or until he took soda. Six months later he began to vomit during the day and more frequently in the early hours of the morning. He had frequent nocturnal pain. X-ray examination revealed a definite duodenal defect. He was admitted to the hospital and placed on a diet of frequent feedings of soft, comminuted food and obtained complete relief. One year later after some dietary indiscretions he had a return of symptoms and on reexamination again showed a duodenal defect. He obtained relief on resuming the original diet. During the last year he had recurring distress every three or four months and was again admitted to the hospital. The child's father and sister had both undergone subtotal gastric resections for duodenal ulcers and another brother had post-prandial abdominal pain.

Case 8. Female, age 15, came to the clinic in 1933 stating that she had abdominal pain for seven years. It appeared in the epigastrium or both lower quadrants of the abdomen, at times was quite severe and was not definitely connected with the taking of food, or accompanied by vomiting. X-ray examination revealed a definite duodenal defect. She obtained relief on an ambulatory ulcer regime and tincture of belladonna. She was seen two years later at which time she was free from pain as long as she was careful with her diet.

In addition to the above mentioned patients is another group whose ages ranged from eighteen to thirty-nine, in whom the symptoms of ulcer appeared in childhood and continued into adulthood. *S. E.*, age 39, male, first noted his distress at the age of 16; *E. M.*, age 27, female, at the age of 12; *N. R.*, male, age 18, at 17. His sister, age twenty-four, began to have symptoms at the age of 18. The father of the last two patients had symptoms of ulcer for years, a severe hemorrhage, and was finally resected for duodenal ulcer with complete relief. In all of the above cited cases the diagnosis was confirmed roentgenologically.

COMMENT

With all the apparent frequency of duodenal ulcer in children, the incidence is still comparatively low. There is no way of telling accurately how many children, if subjected to a roentgenologic examination for minor gastric upsets, would reveal lesions. In the gastro-intestinal clinic only adults are seen and children are referred here on exceptional occasions only. From conversations with some of the staff of the pediatric clinic it would appear that such lesions are found more frequently than before. A careful inquiry into the history of the duration of the symptoms with attention focused on the period of childhood, would undoubtedly uncover a higher incidence than heretofore suspected. That has been our own personal experience since we directed our attention to that phase of the question.

A not unimportant aid in the diagnosis of ulcer is the family history. More and more have we, as well as many others, come to feel that the co-existence of ulcer in two or more members of a family is not merely a coincidence. We have encountered a family of four in whom both parents had undergone operations for ulcer and both children with active ulcers, a family of eight children with six having ulcers, a family of four with three having ulcers, in whom the symptoms began in the second decade of life. If a doubt arises as to the advisability of making a roentgenologic examination in children with mild gastro-intestinal symptoms, a family history of ulcer should be sufficient warrant to recommend it. It is difficult to make any accurate statement of the proportion of the familial to the total number of cases of ulcer; in other words, the importance of the role of heredity. In our experience it would appear to be close to twenty-five per cent. Attention to this subject was called in our previous communication.

The majority of children affected with ulcer seem

to respond readily to an ambulatory form of treatment consisting of frequent feedings of well comminuted bland foods, with occasionally some calcium carbonate or soda and tincture of belladonna three times daily. The outstanding exception was G. K. in the first series whose duodenal lesion bled profusely and was associated with an esophageal one which terminated with stricture formation. The relapses in most cases were due to dietary indiscretions and were readily controlled by a resumption of the proper diet. The one patient with obstructive symptoms was 13 years old when he first appeared at the clinic and 21 when we saw him. He may require surgical attention. It would be interesting to be able to follow up the others to see whether any complications arise that might make surgical attention necessary when adulthood is reached. However, none of the four patients cited in whom the lesions began in childhood or adolescence have so far developed any evidences of obstruction or failed to respond to medical management.

CONCLUSIONS

1. The subsequent course of four of five previously reported cases of duodenal ulcer in children is reviewed.

2. Eight new case reports are submitted.

3. Attention is directed towards the importance of the family history in the diagnosis of duodenal ulcer.

4. Ambulatory management seems to suffice in nearly every patient and complications are comparatively rare.

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Colon Motility: An Experimental Study of the Colon in the Dog*

By

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and

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THIS investigation was stimulated by our unsatisfactory clinical results in the treatment of the so-called "spastic colitis" in the human. Colon motility in man has been for practical purposes limited to fluoroscopic observations. We may conclude that the bowel content appears to be "pushed along" without the aid of peristaltic waves but at irregular and variable times there may occur "mass movements" as described by Hurst (6). The literature on colon motility in the dog was found to be not only extremely sparse but also contradictory in nature. This investigation included a study of motility in the normal colon, the changes of motility in the colon inflamed by chemical irritation, and the effects of drugs commonly used upon the function of irritated bowel.

METHODS

Thiry fistulae in the colons of dogs were made in the following places: 1—adjacent to the cecum, 2—the ascending colon and 3—the transverse colon. The recto-sigmoid as a site for colon fistulae was abandoned because none of our animals survived the surgical procedure.

1. The motility of the isolated bowel segment was studied in the customary fashion by inserting a balloon connected to a water manometer. Bowel contractions were recorded on a revolving kymograph. For the establishment of the normal types of contraction an air filled balloon was used. In the pathologic experiments a water system was used.

2. The gastro-colic reflex was studied in normal dogs which were starved for twenty-four hours. Peristaltic activity of the fistulae was then recorded after which a meal of milk, eggs and syrup was given to the animals. In one series this meal was put into the stomach by tube, and in the other series was ingested normally. In both instances the peristalsis of the fistulae were studied after feeding.

3. While the activity of the fistula was being recorded the dogs were injected subcutaneously with the drugs to be evaluated in order to determine their effect upon colon motility.

4. Inflammatory changes were made in the fistulae by irrigation with mustard oil in an olive oil vehicle. When this was done three times weekly for three to four weeks a pronounced inflammatory colitis resulted. The type of motility of such an inflamed bowel was studied during the activity as well as the regression of the pathologic processes. In addition the effect of atropine sulphate gr. 1/60 upon such an irritated colon was also investigated.

RESULTS

I. Normal Colon Studies. A—In the colon adjacent to the cecum, 425 minutes of recording revealed active peristalsis for 360 minutes. The average duration of a period of peristalsis was 25 minutes, followed by an inactive interval of 5 minutes. The contractions were quite rhythmic, having a rate of 2-3 per minute and an altitude of 18 mm. water. The waves, (Fig. 1-A and B) were peaked, ascending and descending sharply.

B—In the ascending colon 420 minutes of recording showed peristalsis for 300 minutes. The duration of the active periods averaged 22 minutes and the inactive interval 10 minutes. Two varieties of contractions were observed here. The first, type 1, (Fig. 1-C) were rapid, 2-3 per minute, while their amplitude was small, 4-6 mm. of water. The waves were very regular and rounded. The type 2 contractions (Fig. 1-D) were slower, 1 per minute, with an amplitude of 12 mm. water. These contractions were not as regular as the first type and the crest of the waves were flatter, indicating a sustained contraction.

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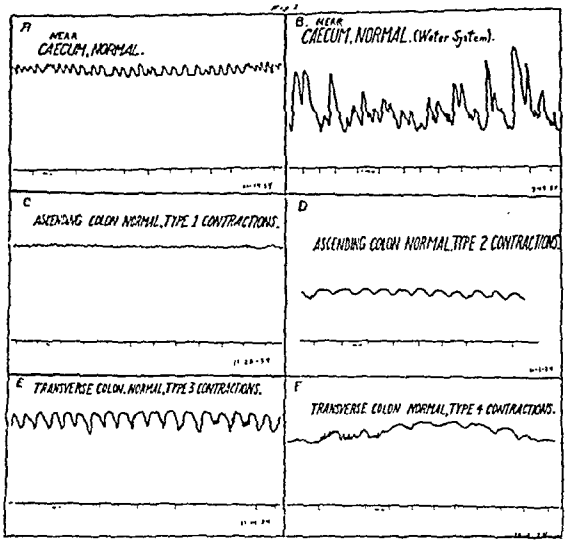


Fig. 1

C—In the transverse colon 375 minutes of recording demonstrated peristalsis for 265 minutes. The duration of peristaltic activity averaged 18 minutes and the rest interval 9 minutes. Two types of contractions were also observed in this region. In the first, type 3, (Fig. 1-E) the rate was slow, 1 per minute, and the amplitude very large, measuring 26 mm. water. The waves were rhythmic, and although the crests were flat, ascent and descent was abrupt. The type 4 wave (Fig. 1-F) was more of a tonus change with irregular, small waves superimposed on the main one. The height of this contraction at its peak was 26 mm. water.

D — Gastro-colic reflex — Meals given by stomach tube neither initiated nor augmented peristalsis in the Thiry fistulae of the cecal area, ascending colon, or transverse colon. When, however, the same type of meals were given by mouth, a marked increase in the rate of peristalsis was seen in the colon adjacent to the cecum within 2 minutes, and longer, sustained contractions were initiated in the transverse colon.

II. Effect of Drugs. Results had to be cautiously evaluated and well controlled because spontaneous periods of initiation and inhibition of peristalsis occurred. Atropine sulphate gr. 1/60, caused complete protracted inhibition of all peristaltic activity in from 9 to 15 minutes (Fig. 2-A). This drug had the same effect when given after pilocarpine. Neither initiation, augmentation, nor inhibition of peristalsis was observed when the following drugs were used: epinephrine 0.3 c.c., insulin 3 units, histamine 1 mg., pilocarpine 6 mg., pituitrin (surgical and obstetrical) 0.5 c.c., morphine sulphate gr. ¼, 1-histidine monohydrochloride (Larostidin) 3 c.c., and phosphate salt of 3-diethylamino-2 2-dimethylpropanol tropic acid ester, (Syntropan) 0.02 gm.

III. Colon Motility and Mechanical Small Bowel Ileus. Eight weeks post-operatively one of the colon Thiry fistula animals was listless and losing weight. Recordings of motility in the fistula at this time demonstrated that the contractions had increased in amplitude from 12 mm. to 44 mm., and the rate decreased from 2.7 to 1.6 per minute, (contrast A and B, Fig. 3). The abnormal contractions persisted until the animal died one month later, when post-mortem examination revealed a mechanical (adhesive band) obstruction of the ileum, with gangrene, perforation and peritonitis.

IV. Experimental Colitis. The acute chemical colitis in a colon Thiry fistula secondary to mustard oil irritation caused an immediate and markedly elevated contraction which persisted for about 2 minutes (Fig. 4-A). Tracings taken after 4 weeks of mustard oil irrigations demonstrated a persistent, increased tonus with contractions whose rate and amplitude were much diminished (Fig. 4-B). Atropine sulphate gr. 1/60 injected into such an animal caused complete cessation of peristalsis and a marked decrease of tonus within 20 minutes (Fig. 2-B). Three weeks after mustard oil irrigations were stopped a tracing of the convalescent colon fistula showed a increase in the rate and amplitude of the contractions, but decrease of tonus (Fig. 4-C). Two weeks later a tracing demonstrated almost complete recovery (Fig. 4-D).

DISCUSSION

Bargen and Larsen (3) and Plant and Miller (8), using balloons in dog colon fistulae reported, respectively, contraction rates of 8 to 10 and 7 to 14 per minute. Three types of contractions were described by Templeton and Lawson (9). These were rapid contractions appearing as a simple curve, slower contractions surmounted by the first type, and tone changes surmounted by both of the preceding. Welch and Plant (10), reported that the muscular activity, of the dog's colon was very irregular, consisting chiefly of marked variations of tonus, with or without superimposed contractions. Our tracings (Fig. 1) demonstrate marked rhythm and rates of peristalsis varying from 1 to 3 per minute, whereas tonus waves surmounted by smaller waves were infrequently seen and then only in the transverse colon.

Our studies indicate that the motility of the colon decreases in an analward direction, confirming at least part of Alvarez's theory (2) of intestinal gradients. In the vicinity of the cecum the greatest activity was observed, the contractions all being rhythmic, peaked and frequent. The tandem balloon studies of Templeton and Lawson (9) reveal that the early part of the period of activity in the proximal colon was accompanied by a delay of contractions analward, while the latter part of the period showing contractions delayed oralward and increased analward. If the dog's colon is physiologically a distal colon, and this is the opinion of many investigators, differentiation of propulsive and nonpropulsive activity becomes a minor consideration because the organ should have

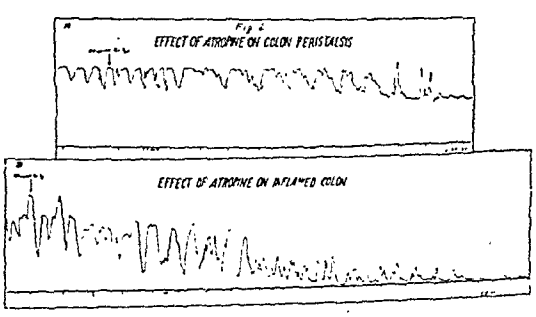


Fig. 2

no need for nonpropulsive movements. Our results show greatest activity nearer the cecum and diminution of activity analward, suggesting that the dog's colon is not a simple distal colon. There is a similarity to the herbivorous animal wherein the area near the cecum shows the greatest activity. This might very well indicate a churning or nonpropulsive activity in the cecal region with the remainder of the organ having as its role, coordinated peristalsis for driving bowel contents toward the anus.

We agree with Welch and Plant (10), in calling the gastrocolic reflex a misnomer. It is really a feeding or appetite reflex. In our studies it produced an increase in the rate of motility near the cecum, but in the remainder of the colon only a prolongation of the individual contractions. This again suggests that the dog's colon does have differentiation of activity in its various components and therefore is not simply a distal colon. We did not experiment with the terminal colon which Templeton and Lawson (9), and Bargen and Larson (3) found almost devoid of activity.

The power of atropine to depress colon motility, even after pilocarpine administration is in accord with the work of Katsch (7), and Hirz (5). This marked inhibitory effect of atropine on the experimentally inflamed fistulae indicates the rationale of its use in humans. We cannot explain why histamine had no effect on the motility of the Thiry fistulae nor why pilocarpine, pituitrin, morphine sulphate, 1-histidine monohydrochloride (Larostidin) or phosphate salt of 3-diethylamino-2 2-dimethylpropanol tropic acid ester (Syntropan) gave no demonstrable results. Our negative experimental findings explain the futility of expecting good clinical results when using these drugs for symptomatic relief.

Alvarez (1) noticed that the injection of turpentine into the iliocecal area caused a diarrhea and rapidly emptying colon. He stated that irritation at any point in the bowel tends to slow the progress of material moving away from it. This theory (Alvarez's Law) would explain the increased colon motility accompanying small bowel ileus. We are inclined to believe that the mechanism is probably an intrinsic bowel reflex rather than a central one.

Alvarez (2) has reported that inflammation of intestinal strips doubled the normal contraction rate. The colon fistulae studied by us did not show this effect. Our graphic demonstration of motility during the production and involution of colitis indicated that an acute irritation simply produced a marked, sustained contraction which relaxed in a few minutes. The chronically inflamed colon was persistently spastic with increased tonus and irregular contractions of small amplitude and insignificant rate change. This finding simulated that of chronic colitis of man,

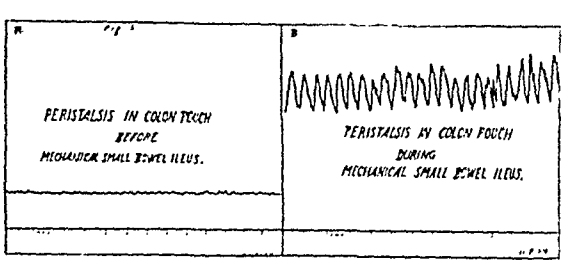


Fig. 3

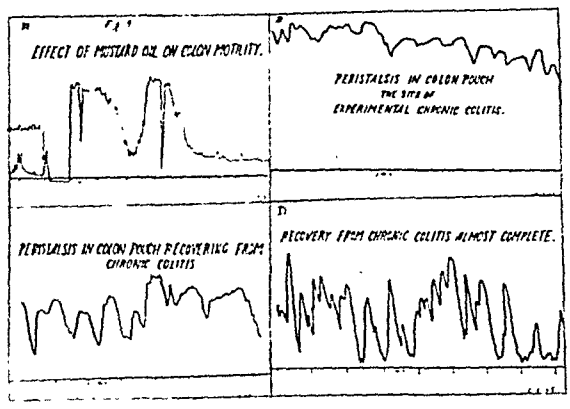


Fig. 4

where the sigmoid is felt to be persistently hard and spastic. Perhaps in man also the contractions are of small amplitude and arhythmic and therefore ineffectual for bowel content propulsion. The tracings showed that the involution of the colitis was characterized by decreased tonus, and waves of increasing amplitude and regularity.

SUMMARY

1. The motor activity of the dog's colon is characterized by rhythmic peristaltic waves, the rate of which vary from 1 to 4 per minute, decreasing in an analward direction. Near the cecum, the contractions are abrupt and of short duration, whereas analward they are less frequent and much more prolonged. Evidence points to differentiation of motility in various parts of the dog's colon, with a marked similarity to the activity of the colon of herbivorous animals.

2. There is no gastro-colic reflex. There is a feeding or appetite reflex to the colon which causes an increase in the rate of contractions near the cecum and marked prolongation of peristaltic waves distally.

3. Atropine sulphate will completely inhibit the activity of a normal or inflamed colon. Histamine, pilocarpine, insulin, pituitrin, morphine, Larostidin and Syntropan were found by us to be without demonstrable effect on the motility of the colon.

4. In one animal mechanical ileus in the small bowel caused a marked increase in the motility of the large bowel.

5. A chemical irritation of the colon caused a spastic contraction which relaxed after a few minutes. Peristalsis in a chronically inflamed colon is characterized by increased tonus and irregular, feeble contractions. With healing of the inflamed colon abnormal peristalsis slowly disappeared and function again became normal.

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The Value of Histidine in Prevention of Experimental Ulcer in Dogs*

By

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AS is well known, the Mann-Williamson operation of surgical duodenal drainage produces peptic ulcer in almost 100% of dogs (1). Weiss and Aron (2), in 1933, reported that histidine injected daily prevented this development of ulcer. They performed the Mann-Williamson operation on five dogs. Two, used as controls, developed ulcer. Three were given daily injections of histidine-tryptophan starting immediately after the operation. These three animals were sacrificed five, six, and ten weeks, respectively, postoperatively. No ulcers were found in any of these three animals. As a result of further experimentation (not on Mann-Williamson dogs) they concluded that histidine alone had a protective value against ulcers. Postulating that histidine prevented ulcer, they began treating ulcer patients by injections of this substance intramuscularly. There have appeared, since their report, approximately 100 clinical papers (3) generally favorable to the effect of histidine upon the treatment of peptic ulcer in man. The more important ones were summarized by Kirby Martin (4), and by Sandweiss (5).

Recently Flood and Mullins (6) repeated Weiss and Aron's work (which up to this time had been the sole experimental basis for this extensive clinical literature). They used 17 dogs: five were kept as controls and the remaining 12 were injected with daily doses of varying amounts of histidine (Larostidin. Dosage: 4.8 to 10.9 mg. of histidine per kilogram body weight). The five controls developed ulcer in from 51 to 104 days, four of them with perforation, one a shallow ulcer. Of the 12 dogs receiving histidine, five died without evidence of ulcer in from 40 to 82 days. Six showed ulcers, either large, perforated, or multiple, dying in from 51 to 94 days. The remaining animal died of intestinal obstruction on the 56th day, and showed a small superficial erosion of the first portion of the jejunum. Thus 45% of the animals receiving histidine failed to develop ulcers.

We have recently also repeated these experiments. Our method was as follows:

EXPERIMENTAL

The standard Mann-Williamson operation was done. The pylorus was sectioned and the distal end was inverted. The jejunum was divided about 10 cm. beyond the ligament of Treitz. Anastomosis between the stomach and the distal end of the jejunum was then done, generally end to side, though occasionally end to end. The lower anastomosis between the proximal jejunum and terminal ileum was always end to side, and about 20 to 30 cm. from the ileo-cecal valve. Fine silk was used throughout, with no clamps. The dogs were starved 24-48 hours before operation. Ether anaesthesia was used. They were given water as tolerated for four days postoperatively (plus saline subcutaneously as needed, 3-4 days) and then placed on a diet consisting of finely chopped hamburger, bread and milk. The reason for this was to allow no roughage.

Histidine (Larostidin) injections were given twice daily, in the same amount (1 c.c.) to each animal.* The injections were started either before or within a few days after the operation, as indicated on the table. Fourteen dogs received histidine. Twelve received none, and were used as controls.

TABLE I

Histidine treated dogs

Dog	P.O. Duration of life (days)	Histidine started (days of OR)	Results
1	29	4 days P.O.	Small ulcer with low grade inflammatory reaction at base.
2	10	2 days P.O.	Crescent shaped ulcer with inflammatory changes.
3	195	5 days P.O.	Perforated ulcer.
4	55	1 day before OR	Perforated ulcer.
5	43	day of OR	Perforated ulcer.
6	19	day of OR	Death from Distemper. However, there was marked localized jejunitis with edema and clubbing of villi and inflammatory infiltration of wall. Early ulcer.
7	45	5 days P.O.	Perforated ulcer.
8	121	2 days P.O.	Small superficial ulcer.
9	83	3 days P.O.	Perforated ulcer.
10	277	1 day P.O.	Perforated ulcer.
11	33	2 days P.O.	Death from intussusception. *No* ulcer.
12	101	day of OR	Perforated ulcer.
13	16	day of OR	Perforated ulcer.
14	58	1 day P.O.	Profuse hemorrhage—small punched out ulcer.

RESULTS

Of twelve controls, all died with ulcers.

Of fourteen dogs, receiving histidine, eight died of peritonitis following perforation of jejunal ulcers.

*Two c.c. of Larostidin daily, representing 80 mgm. of histidine was given per day to each dog. The average weight of the animals was 7-16 Kilo. (15-35 lbs.) and this dosage was therefore approximately 2 to 3 times the dose per Kgm. body weight suggested and used in the treatment of patients with peptic ulcer. Part of the Larostidin was furnished through the courtesy of Hoffmann-La-Roche Co.

*From the Laboratory of Experimental Surgery, Harper Hospital, Detroit, Mich. Aided by a grant from the Mendelsohn Fund.
Submitted December 11, 1936.



Dog No. 12 died 101 days post-operatively. 2 c.c. of histidine monohydrochloride (Larostidin) were injected daily beginning with the day of operation to the day of death. Perforated ulcer.

Another had profuse hemorrhage from a small deep ulcer. Another, dying on the 121st day, showed a superficial ulcer. With one exception, these 10 animals *lived more than 40 days after the operation.* Two dogs died 10 and 30 days post-operatively and showed small ulcers with low grade inflammatory reaction at bases. One died 19 days post-operatively showing marked localized jejunitis with edema and clubbing of villi and inflammatory infiltration of wall considered as an early ulcer. Only one died (on the 33rd day) without ulcer formation. Autopsy revealed intussusception as the cause of death. We believe that this dog would also have developed an ulcer had intussusception not developed, and death ensued.

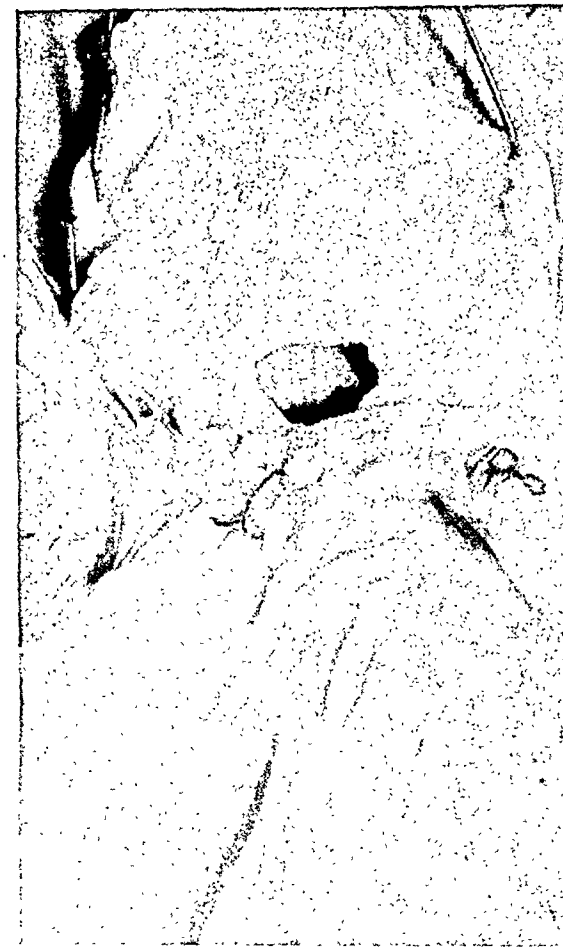
Thus, 13 or 93% of histidine treated animals showed ulcer formation. If they lived longer than one month, they had typical chronic perforating ulcers. If they died within the first month, they showed small ulcers with inflammatory reaction at bases (two) or localized jejunitis (one). One dog died 16 days post-operatively from a perforated ulcer. All of these lesions were just distal to the line of union between stomach and jejunum. They did not involve the line of anastomosis and never began more than one cm. distant from this line, and they showed little tendency to fibrosis and repair. There was no gross or microscopic difference between the ulcers in control and treated animals.

It should be noted (Fig. 1) that, whereas all of the twelve control dogs that died of ulcer, died within 16 weeks, post-operatively, only ten of our thirteen histidine treated dogs died with ulcer within the same period of time. The remaining three histidine treated dogs that died with ulcer, died later than the maximum survival of the control dogs. (One died 17 weeks, post-operatively; one, 28 weeks post-operatively and the third, 39 weeks after the operation). It may therefore be said that although histidine neither prevented ulcer formation nor healed the ulcers after they had formed, three histidine treated dogs lived longer than the control dogs, although they all subsequently died with ulcer. In our opinion there is no significant difference between the curves of treated dogs and controls—which we believe would be the opinion of those who have had extensive experience in Mann-Williamson dogs.

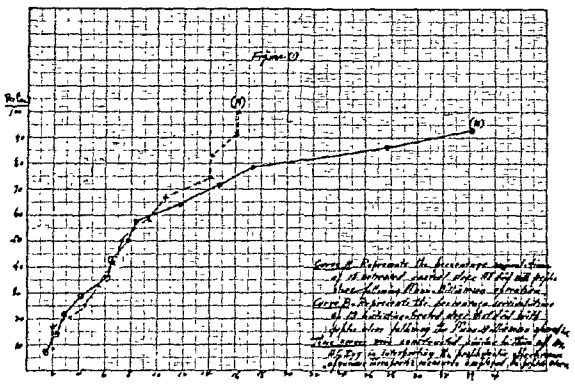
EXPERIMENTAL WORK OTHER THAN ORIGINAL WEISS-ARON EXPERIMENT

Fontes and Bauer (8) repeated the experimental work of Weiss and Aron but instead of daily intramuscular injections of histidine gave histidine orally in doses of from 0.25 to 0.5 gm. daily to 100 dogs. They report that 30% of their dogs did not develop ulcer. These authors, however, question histidine as being the sole factor in the non-appearance of experimental ulcer.

Recently Stalker (12) of the Mayo Foundation has tried the protective effect of various substances on experimental ulcers in dogs, produced by cincophen. All control animals developed a chronic ulcer within 30 days. The dogs treated



Dog No. 13 died 16 days post-operatively. 2 c.c. of histidine monohydrochloride (Larostidin) were injected daily beginning with the day of operation to the day of death. Perforated ulcer.



by standard diet alkaline regime developed no chronic ulcer. Those on milk developed only a superficial ulcer. Mucin protected 50% from the development of a chronic ulcer. "Every dog treated with Larostidin developed a chronic ulcer."

Volini and McLaughlin (9) produced gastric ulcers in rats by repeated injections of histamine dihydrochloride as well as by the use of repeated histamine enemata. They report that these experimental ulcers did not occur when the animals were protected by previous injections of histidine monhydrochloride. However, Matzner and Windwer (10) were unable to prevent with histidine injections, experimental gastric ulcers in rats produced by their pepsin-hydrochloric acid method (11). On the contrary, by injecting histidine daily into otherwise normal rats, using no ulcer producing agent, 50% developed ulcer. They suggest that histidine may be converted into histamine by simple decarboxylation and thus produce ulcer (histamine is a well known ulcer producing agent).

THE HISTIDINE DEFICIENCY THEORY OF PEPTIC ULCER

Weiss and Aron assumed that peptic ulcer was the result of a deficiency or absence of the amino acid, histidine.

Martin (4) points out that histidine is a constitutent of most of the simple proteins and may be obtained from a great variety of foodstuffs, most important of which are beef, eggs, fish and milk. He says: "there is no convincing evidence from feeding experiments that a deficiency of this substance (histidine) can be produced in animals." Mitchell and Hamilton (7) state that the presence of histidine in foodstuffs is so universal that the exclusion of histidine-producing foods would make a diet incomplete in other indispensable dietary factors.

Flood and Mullins (6) in repeating the experimental work of Weiss and Aron investigated a variety of factors in blood chemistry, local chemistry and pathology, following surgical duodenal drainage, to see whether there was any difference between controls and histidine treated animals. They found marked decrease in serum protein and bicarbonate with an accompanying rise in serum chloride following surgical duodenal drainage. Blood amino nitrogen shows wide fluctuations and some tendency to decrease. There is no tendency to an increase in gastric HCl concentration following operation. There is, in fact, late subacidity. All animals showed progressive secondary anemia. All of these changes were exactly parallel in both control and treated series. In addition, the local amino nitrogen content of the jejunal and antral portions of the stomach were determined, since it had been claimed that histidine might exercise a protective effect against jejunal ulcer by some mechanism involving local increase in tissue amino nitrogen. There was no significant difference between the two groups.

Flood and Mullins further report that pathologically, there was no evidence of gastritis. There were frequent submucosal hemorrhages in the small intestine and colon, and "at times the villi of the upper jejunum appeared shrunken and the surface of the intestine has lost its normal velvity appearance." There was no evidence of fibrosis in the wall of the jejunum beyond a short distance beyond the bed of the ulcer. These changes were identical in both groups, except that "atrophy of the jejunal mucosa was less marked in some of the dogs receiving histidine than in the controls." Thus, although 45% of the animals treated with histidine failed to develop ulcer, no substantiation of the amino acid deficiency theory of histidine action was obtained.

The difference between our results and those of Flood and Mullins may possibly be explained by the fact that in their experiments, the duodenum was divided at a point about one cm. beyond the pylorus. In the original Mann-Williamson operation as well as in our experimental work, the section was made directly at the pylorus. The possible protective mechanism of the duodenal mucosa was thus entirely eliminated. Ivy and Fauley (13) reported that in three of a series of 11 Mann-Williamson dogs, no ulcers were found when the duodenum was sectioned leaving a small stump attached to the pylorus. The small stump of the duodenum which Flood and Mullins left attached to the stomach may account for the 45% protection against ulcer in their dogs.

It appears that there is no experimental evidence that a deficiency or absence of histidine is the cause of peptic ulcer. Recent clinical reports substantiate the above experimental work. Kirby Martin (4) states that when symptom-free intervals result "the clinical improvement succeeding histidine-hydrochloride therapy in acute peptic ulcer appears to be symptomatic and transient." Sandweiss (14) states that

TABLE II
Control dogs

Dog	P.O. Duration of life (days)	Results
15	31	Perforated ulcer.
16	113	Perforated ulcer.
17	51	Perforated ulcer.
18	66	Three ulcers.
19	38	Circular ulcer 1 cm. extending into muscularis.
20	13	Perforated ulcer.
21	46	Large ulcer.
22	98	Perforated ulcer.
23	74	Perforated ulcer.
24	99	Perforated ulcer.
25	113	Perforated ulcer.
26	13	Perforated ulcer.

results obtained with injections of distilled water compare favorably with those of histidine, reporting that in a series of 22 patients treated with daily injections of distilled water, 13 became symptom free. Flood and Mullins (15) report similar good results in

8 of 12 patients treated with daily injections of saline.

SUMMARY

We are unable to corroborate the original experimental work of Weiss and Aron, that histidine has a protective value against peptic ulcer produced in dogs by the Exalto-Mann-Williamson operation. Of fourteen dogs receiving daily injections of histidine, following surgical duodenal drainage, (2 c.c. Larostidin daily which contains 80 mgm. of histidine) 13 or 93% showed ulcer formation. Of 12 controls, all developed ulcers.

The histidine deficiency theory of peptic ulcer is discussed. There is no evidence that a deficiency or absence of histidine is the cause of peptic ulcer.

Note: The authors are indebted to Dr. A. C. Ivy for his valuable advice in this work; also to Dr. Plinn F. Morse, Pathologist, Harper Hospital, Detroit, Michigan, for the gross and microscopic examinations of the specimens obtained at autopsy. Mr. I. Silver assisted in this work.

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Experimental Production of Polyposis of the Colon in Rats*

By

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and

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IN attempting to produce duodenal ulcers in rats by dietary means, we tried feeding a mixture of 200 (parts by weight) pulverized cellulose, 43 casein, 43 corn starch, 5 dry yeast powder, 5 alfalfa meal and 4 salt mixture. This diet was intended to supply a large amount of roughage, a relatively high proportion of protein and practically no fat. Sixteen days after eight rats were placed on this diet one rat (Rat 740) died. Upon autopsy, numerous ulcers were found in the prostomach. The main stomach was slightly eroded. The duodenum was normal. A few lesions were found in the small intestine and cecum, and inflammed areas, small papilli and larger sessile polyps were found in the colon (Fig. 1). The largest polyp (Fig. 2) snugly filled a sharp and relatively deep depression in the side of a compact fecal pellet, which consisted mainly of pulverized cellulose. The polyp served to anchor the pellet firmly and the combination apparently formed an intestinal obstruction which led to the death of the animal. The feces showed that this rat had eaten some of the above diet but the ulceration of the prostomach and a decline in weight from 306 gm. at the beginning to 169 gm. at death indicated that this rat practically starved to death (1).

Before Rat 740 was autopsied, we autopsied 716 other rats. These rats were fed a wide variety of diets which were primarily used to produce lesions in the upper part of the digestive tract (1). However, we found small papilli (one or more) in the colon of 17 of these rats and the polypoid nature of these papilli became clear when the colon of Rat 740 was observed. The colonic papilli occurred as follows among the 716 rats: Eight cases among 88 rats fed diets including a slightly fibrous type of cellulose flour; 6 cases among 40 rats fed diets including ground bran; 1 case among 123 rats fed diets with coarse bran; 1 among 14 rats fed diets with sawdust; 1 among 6 rats fed a diet without roughage but deficient in vitamin B, and none among 445 rats that were either starved, fed diets without roughage or diets including vegetables, agar, India gum or mineral oil. This distribution of polypoid lesions made it evident that the polyposis in Rat 740 was mainly due to the pulverized cellulose included in the diet and it also suggested that pulverized inert materials in general might cause polyposis. Besides this, our data suggested that the relatively high protein content of the

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diet fed to Rat 740 was another factor in the production of severe polyposis in that case.

In order to study the mechanism of polyp production more closely, 281 additional rats were fed diets including from 5 to over 95% inert materials, such as kaolin, pulverized cellulose, barium sulphate, talcum powder and flaked cellulose (ground artificial straw). The protein content of these diets varied from 18 to over 80% (of the total nutritive ingredients) and cod liver oil was often used in place of the alfalfa meal which was used in the diet fed to Rat 740. The diets were fed for periods ranging from 2 days to over 6 months. In addition to this, some of the diets were fed to 36 mice for comparison with the results obtained on rats.

The autopsies of the 281 rats showed that polyposis of the colon occurred as follows: In 36 (37%) of 96 rats fed kaolin; in 40 (33%) of 122 rats fed powdered cellulose; in 9 (31%) of 29 rats fed barium sulphate; in 1 of 3 rats fed talcum powder; in 3 of 7 rats fed granular cellulose (cellophane ground in a hammer mill); in 1 rat that was previously fed barium sulphate among 10 rats fed flaked cellulose (artificial straw cut up in a meat chopper); and in 2 rats among 13 fed kaolin plus sand. Nine rats of the kaolin plus sand group died as a result of the irritating effects of the sand. Talcum powder caused diarrhea in some rats. Seven of the younger rats on barium sulphate also developed diarrhea and showed toxic symptoms. Bismuth subnitrate could not even be used as an inert material because it proved to be highly toxic to the rats; it was evidently acted on by the acid in the stomach.

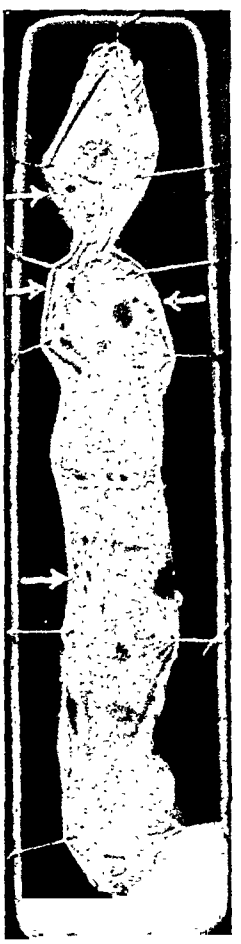


Fig. 1. Showing inflammed areas, small papilli and larger polyps in colon of rat fed a diet including 67% pulverized cellulose—16 days.

The degree of polyposis ranged from a single small papilla to two or more larger sessile polyps (Fig. 3) and one case of a pedunculated polyp (Fig. 4). The pedunculated polyp was found in the rectum of a rat (*Rat 810*) that was fed for 29 days with diets consisting of 50 (parts by weight) casein, 30 corn starch, 5 corn oil, 5 cod liver oil, 6 dry yeast powder, 4 salt mixture and either 200 kaolin or 80 kaolin, 80 barium sulphate and 40 pulverized cellulose. In some rats, polypoid lesions were found in the terminal ileum and/or cecum (Fig. 3). Polyps also developed in some rats that were not yet weaned. These rats licked or sucked up a dry mixture containing kaolin that was sprinkled in the nests for this purpose. The youngest rat with colonic polyposis (marked) was 14 days old and was exposed to kaolin only 48 hours. The greatest degrees of polyposis occurred when the diets contained from 60 to 75% pulverized inert material (from 150 to 300 parts inert material to 100 parts nutritive ingredients) but some polyposis was observed in rats fed as little as 8% pulverized inert material. A protein content of from 30 to 50% of the nutritive ingredients in the diet also seemed to be best for polyp production.

The pulverized inert materials were found to have a striking effect upon the form of the feces and this suggested their rôle in the development of polyps. Figure 5 shows fecal pellets passed by rats fed various inert materials. As indicated, the pellets produced by feeding pulverized materials often contained sharp depressions, pits or gas-pockets while flake-like materials (as well as fibrous materials, vegetables and agar) usually gave rise to fecal pellets without such pits or with only shallow depressions. The pits or depressions in the pellets frequently contained blood and pellets with blood-stained pits were passed at some time or other by about 90% of the rats fed pulverized inert materials. In fact, the only exceptions seemed to be rats with a diseased cecum and/or an irritable colon in which abnormally large amounts of mucus were secreted. Pellets with blood-stained pits were passed as early as four hours after some hungry rats were placed on a diet including kaolin. Sometimes as many as six small pits in a single pellet would contain blood but many pits contained no blood.

Observations were made, after laparotomy, on the colon of some rats with pitted fecal pellets *in situ* and this showed that bleeding into pits was due to suction of the colon into the pits and small deep pits caused suction more often than large shallow pits. The first impression usually was that the colon was perforated at such sites but closer examination always proved that the colon was only sharply drawn into the pits. The pits that did not become blood-stained were generally well filled out with gas and did not cause any suction on, or distortion of, the colon. It therefore seems that all of the pits represent gas-pockets or sites in which gas was trapped while the pellets were in process of becoming permanently formed, dehydrated



Fig. 2. Section of one of the sessile polyps shown in *Fig.* 1.

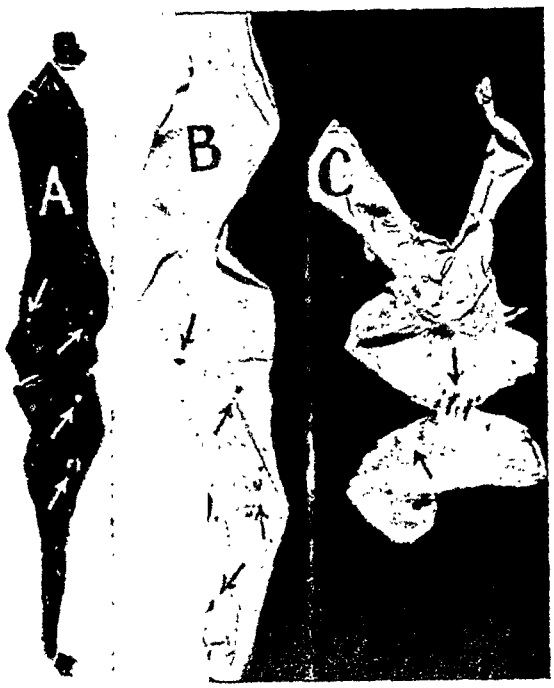


Fig. 3. Showing colonic and cecal polyposis in rats fed diets including (A) 67% barium sulphate—18 days, (B) 75% kaolin—15 days and (C) 75% barium sulphate—5 days.

or "set"—like plaster of Paris. When the gas either escaped, was pushed out of the pits or was adsorbed by the dehydrating pulverized material, the wall of the intestine was drawn in and inflammation and bleeding occurred. It was observed that the empty or suction-creating pits generally left inflammed streaks in the colon which marked their course of passage. Sometimes, more highly inflammed spots appeared along these streaks and indicated where such pits (pellets containing them) halted for longer periods. Mucosal bleeding was thus often occasioned without the development of polyps. The blood evidently helped to fill out the pits, reduced the suction and released the mucosa. Polyps were apparently formed when prolonged or intense suction led to more marked mucosal distortion and submucosal bleeding. Submucosal accumulations of blood evidently helped to keep the mucosa raised like a blood blister. Variations in susceptibility to mucosal distortion and submucosal bleeding may also explain why some rats seemed to develop polyps more easily than others. The pedunculated polyp was very likely the result of repeated peristaltic traction on a well formed sessile polyp. The larger polyps tended to cause intestinal obstruction. Small polyps or papilli and inflammed areas or streaks apparently healed rapidly and many rats were found to have rough or leathery sites in the colon which were probably sites of repeated bleeding and/or polyposis.

Our observations on mice were carried only far enough to satisfy us that the results were similar to, but, in our short experiments, less striking than the results obtained on rats. A few tests were made on guinea-pigs and rabbits but the diets which were tried caused diarrhea after being used a few days. However, the senior author of the present paper also tried various inert materials and felt that the results obtained on rats at least explained why pulverized materials in general proved to be highly unsatisfactory when used alone as a source of bulk in the diet.

Long, Kolmer and Swalm, who already repeated some of our rat feeding experiments (2), intimated that we believed that pulverized inert materials cause polyposis by inducing intestinal stasis but this does not quite represent our view. Pulverized inert materials indeed tend to cause more or less constipation, even in

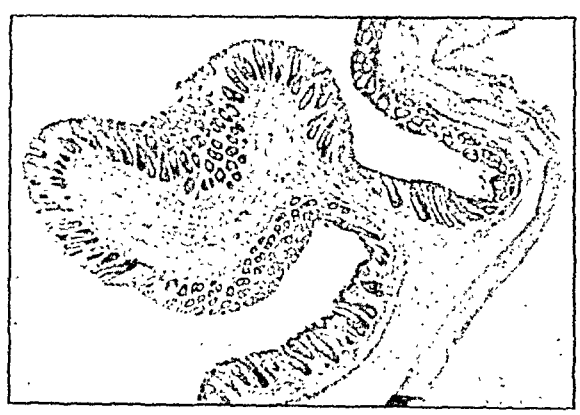


Fig. 4. Section of pedunculated polyp found in rectum of a rat fed a diet including 67% pulverized inert material (mainly kaolin)—29 days.

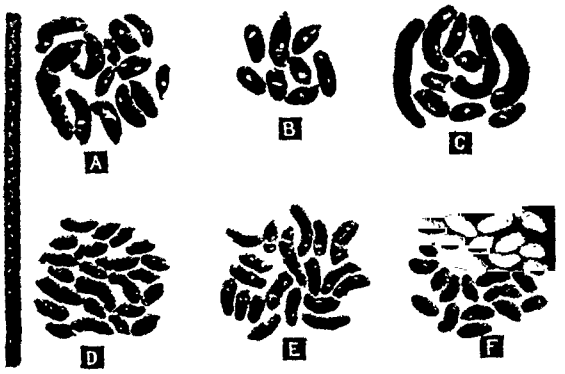


Fig. 5. Types of fecal pellets passed by rats fed diets including from 50 to 80% inert material in the form of (A) kaolin, (B) kaolin plus India gum, (C) barium sulphate, (D) pulverized cellulose, (E) powdered cellulose acetate and (F) flaked cellulose.

rats, by giving rise to relatively hard fecal pellets. The difficulty of passing such pellets was often indicated by the fact that well formed pellets (without pits) were often blood-stained at the posterior end—the end passing last. The bleeding was evidently occasioned by the great effort required to pass such pellets. However, the type of stasis which we believe was often an important factor in the development of polyposis in our rats was a more acute stasis which was mainly due to a decreased food intake. For instance, a few days after Rat 740 was placed on the polyp-producing diet (May 31, 1931) the weather suddenly became extremely hot. As a result, Rat 740 and many other rats ate practically nothing for a day or two. An acute stasis of pellets with accidentally suitable pits evidently then occurred in Rat 740 and the process leading to polyp formation was able to operate without interruption until some degree of intestinal obstruction was produced.

Later, we tried to repeat the conditions that seemed to cause the marked development of polyps in Rat 740 by transfering other rats from cool surroundings to an electrically heated room, after starting them on a diet including pulverized inert material. We believe that we thus obtained far better results than we could have obtained by depending upon favorable changes in the weather but in most cases the results were not striking. We now believe that we failed to get better results because the humidity of our hot room was not controlled and was often low and the artificial heat did not interfere as much with the food intake as the sultry weather which followed the cooler weather of spring. Besides this, we used younger rats in most of our later work and younger rats eat more continuously. We also tried to produce intestinal stasis by restricting the food intake periodically but this made the animals restless and did not serve the purpose as well as sultry weather. In addition to this, we fed some rats pulverized materials with diets deficient in vitamin B, in the hope that this would produce the desired stasis, but again the results were unsatisfactory. The stasis due to vitamin B deficiency did not seem to be a sufficiently acute type. Nevertheless, we believe that the single case of polyposis which we observed among our early autopsies in a rat that had not been fed pulverized inert material was partly due to stasis caused by a vitamin B deficiency. Incidentally, this case shows that polyposis can occur without the use of any form of inert material and our opinion is that pulverized materials simply serve to greatly increase the incidence of intestinal stasis and of fecal conditions which cause intestinal bleeding and/or polyposis under more common conditions.

SUMMARY

Various degrees of polyposis of the colon were produced in 86 (34%) of a group of 250 rats fed diets including pulverized inert materials (kaolin, barium sulphate, talcum powder and pulverized cellulose). Bleeding of the colon occurred in about 90% of the 250 rats.

Intestinal stasis together with fecal conditions producing suction or traction upon the intestinal wall are believed to lead to the development of polyposis.

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Clinical Disorders with Associated Hepatic and Renal Manifestations, with Especial Reference to the So-Called "Hepatorenal Syndrome"*

By

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and

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IT has long been recognized that reciprocal physiological relationships exist between the functions of the liver and the kidney. Their clinical importance, however, has not been fully appreciated. It can be acknowledged that infections and intoxications may simultaneously injure the liver and kidney, and also that renal disease or dysfunction may expose latent liver disease. Recently, a type of renal failure has been linked with trauma to the liver or surgical operations on the biliary tract (28, 32-36, 54). Uremia was

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TABLE I

Urinary output and chemical findings in the blood in Case 2

Day of Illness	4	5	6	7	8	10	12	13	16	19	24	35
Urinary output c.c.	0	0	30	30	30	1210	1385	2425	925	1330	810	—
Urea nitrogen mgm./100 c.c.		23		39	85	146	180	187	81	64	25	12
Amino acid N. mgm./100 c.c.						9.0		8.2				
Plasma chloride mgm/100 c.c.		515			570		500					550
Icterus index					15					7		
Van den Bergh bilirubinemia mgm./100 c.c.		pr. pos. 4.5			del. pos. 0.7					neg. 0.2		
CO_2 vol. per cent								45				47
Cholesterol, total ester fraction, mgm./100 c.c.		300 75			290 72				234 0	190 45		
Sugar mgm./100 c.c		140			100	145		160	185			

Fever between 100.2° F. and 101.6° F. up to 8th day. Normal thereafter until 24th day when parotitis developed.

attributed to renal lesions claimed to be due to the action of specific (28, 33-36) or non-specific (13, 2) nephrotoxic agents liberated from necrotic or infected liver tissue.

The clinical label, "hepatorenal syndrome," has been receiving increasing and indiscriminate usage, on the one hand, to designate all types of disorders in which both organs are involved, and on the other hand, to indicate a special type of case, on the false premise that a specific clinical entity exists.

A comprehensive study of clinical and experimental material in the literature and of cases observed by us has helped clarify the matter. A basis for the classification of the types of cases which have associated disorders of the liver and kidney was evolved.

CLASSIFICATION

The basis for classification depends on etiology and also on the temporal relationship between involvement of the liver and kidney.

I. Systemic Disorders Involving Liver and Kidneys.
   - A. Infections—Spirochetal Jaundice (Weil's Disease).
   - B. Intoxications — Apiol; Chloroform; Thyrotoxicosis; Cantharides (48); "Dioxan" (5); Pregnancy; Blackwater Fever; Transfusion Anuria with Liver Necrosis (12).
   - C. Localization of Systemic Diseases of the Liver and Kidneys
     1. Erythroblastosis.
     2. Generalized Arteritis (see Fig. 1), Periarteritis Nodosa.
     3. Diseases of the Hematopoietic System.

II. Primary Liver Disease with Renal Manifestations.
   - A. Liver Degeneration with Anuria, Oliguria and Azotemia.
   - B. Traumatic Necrosis of the Liver with Secondary Necrotizing Nephrosis.
   - C. Biliary Tract Diseases with Anuria.
     1. Without Surgical Procedure.
     2. Following Surgical Procedure.
   - D. Latent Liver Disease Exposed by Alterations in Renal Function.
   - E. Neoplasms of the Liver and Bile Passages with Anuria.
   - F. Hydatid Disease of the Liver with Secondary Necrotizing Nephrosis.
   - G. General Infections with Jaundice, Anuria, and Azotemia.

III.
   - A. Primary Renal Disease Complicated by Hepatic Disease
   - B. Diseases of the Liver and Kidney Caused Mechanically. Obstructive Jaundice Due to Enlarged Kidney.

IV. *Metabolic.*
   - A. Glycogenic Hepatonephromegaly (von Gierke's Disease) (29).
   - B. Cystinuria and Jaundice.
   - C. Addison's Disease with Azotemia and Jaundice (30).

An attempt was made to elucidate the circumstances responsible for the appearance of renal manifestations, i.e. oliguria, anuria, azotemia, renal lesions, in the group of cases designated as belonging to the hepatorenal syndrome. The following phases of the matter were considered:

1. The role played by surgical procedure, anesthesia, and jaundice.
2. The significance of anatomical and functional changes in the kidney.
3. The importance of the function of the liver in the regulation of water and mineral balance.
4. The relationship of this group of cases to other clinical disorders with analogous renal manifestations but without hepatic and biliary tract disease.
5. The existence of a specific relationship between the liver injury or infection and renal lesions or manifestations: The question of a specific form of intoxication?

THE ROLE OF SURGICAL PROCEDURE, ANESTHESIA AND JAUNDICE IN THE PRODUCTION OF THE RENAL MANIFESTATIONS

The possible role of surgical intervention in precipitating the events which lead to renal disturbances was suggested by the picture of renal failure which occurs not uncommonly following procedures on the biliary tract and then not due to shock, vomiting or dehydration. This picture occurs only rarely following other types of operations. A direct relationship between the

procedure and the ensuing events was accepted by surgeons. At first, the anesthesia and its effect on liver function was incriminated. However, cases occurred when spinal anesthesia was employed. Errors in operative technic, such as accidental ligation of an anomalous hepatic artery branch were also suspected but necropsy findings in fatal cases did not substantiate the suspicion. Sudden decompression of the biliary tract in cases of biliary obstruction were blamed for hepatic and renal failure. However, the entire picture has occurred in cases of gall stones without jaundice.

Cases have come under our observation and others have been reported in the literature indicating that surgical and adjunct procedures are unnecessary in the production of the renal manifestations. These may be considered under the following categories:

1. Acute and subacute atrophy of the liver with jaundice, anuria and azotemia.
2. Biliary tract disease, usually with cholangitis.
3. Malignancy of the liver or biliary tract with anuria and azotemia.
4. General infections and intoxications with jaundice, anuria and azotemia.

CASE REPORTS

Group 1. Liver Atrophy. Case No. 1. No. 376003, E. S.—Subacute Yellow Atrophy of the Liver with Anuria and Uremia. Biopsy of Kidney. Necrotizing Nephrosis.

A Negro, aged 28 years, with a history of lues, developed a dull pain in his lower back, chilliness, fulness in the epigastric region, fever, nausea, vomiting and diarrhea. Jaundice was first noted in the hospital, when he was admitted to the service of Dr. B. S. Oppenheimer. Edema of the eyelids persisted throughout the illness. The systolic blood pressure rose to 150 millimeters of mercury. The urinary output rapidly diminished (30 c.c. in 24 hours). The urine contained albumin, leucocytes, and erythrocytes. The blood Wassermann reaction was 4 plus. Blood analyses showed a rise in urea nitrogen to 143 milligrams per 100 cubic centimeters; plasma chlorides 490, 410 and 455 milligrams (hypochloremia); carbon dioxide combining power 47 volumes per cent, creatinin 9 to 20 milligrams, and proteins 7.2 per cent. The blood volume was slightly reduced to 61 cubic centimeters per kilogram. The blood icterus was 150 and bilirubin 8 milligrams per 100 cubic centimeters.

Intravenous glucose therapy and decapsulation of the kidneys did not produce a decrease in azotemia. The patient lapsed into semi-stupor and died in a convulsion.

The necropsy revealed subacute liver atrophy. The renal findings confirmed the histological findings reported by Dr. Paul Klemperer on biopsy material (Fig. 2A and B). Severe tubular degeneration with regeneration and acute inflammation of the stroma secondary to the tubular damage was noted. Leucocytes and casts were present in the lumen of the tubules. Most glomerular tufts were intact save for degeneration of the outer capsular epithelium. The general picture was that of a degenerative nephrosis secondary to the liver degeneration. Careful chemical analysis eliminated potassium chlorate and mercury poisoning. The biopsy findings indicated that the renal findings were not the result of postmortem change.

Group 2. Biliary tract disease. Case No. 2. No. 320978, C. U.—Acute and Chronic Cholecystitis, Cholelithiasis, Chronic Cholangitis with Jaundice, Anuria, Azotemia.

A female, aged 53 years, was admitted with a history of pain in the right hypochondrium, nausea, vomiting, anorexia, pruritus, and constipation for a period of three days. Twenty-four hours after admission she ceased voiding urine and became slightly icteric. A huge tender mass was felt in the right hypochondrium and considered to be a swollen liver. The stool contained bile. The urine contained no bilirubin. The patient was anuric for 72 hours, then began to void an ounce of dilute urine daily. The blood urea nitrogen mounted from 23 milligrams per 100 cubic centimeters steadily to 187 milligrams, despite establishment of diuresis of 2425 cubic centimeters on the thirteenth day. On admission, the blood bilirubin was 4.5 milligrams per 100 cubic centimeters. In three days this dropped to a latent jaundice with an icterus index of 15. The bromsulphalein test showed a normal result. Tyrosine was not demonstrated in the urine by the tyrosinase method (42). The urinary output and chemical findings in the blood are tabulated in Table I.

After 24 days of high carbohydrate diet and fluid intake the azotemia disappeared. The size of the liver receded to normal after the first week in the hospital. During convalescence, the patient developed a suppurative parotitis with staphylococcemia. This proved fatal despite surgical drainage. These circumstances afforded the opportunity of making observations on a subject who had just recovered from a combination of events ordinarily described as the "hepatorenal syndrome."

The cause of death revealed by necropsy was a staphylococcic endocarditis complicating the parotitis. An acute and chronic cholecystitis, gall stones, and chronic cholangitis was found. The gall bladder was huge, filled with stones, and markedly thickened. The sudden change in size of the liver during life could not be explained by the pathological findings. There was no microscopic evidence in the liver and kidney to account for the clinical picture. Apart from some minor changes in the nuclei of some of the liver cells, the liver appeared to be normal.

DISCUSSION

The *outstanding features in this case* were the adequate fluid intake by mouth throughout the course of events, the absence of surgical intervention, initial slight hypochloremia and normal blood chlorides thereafter, and the progressive increase in azotemia despite diuresis and adequate fluid intake by mouth. A Volhard concentration test indicated isosthenuria with specific gravity fixed at 1.008 and 1.010.

The elevation of amino-acids in the blood may indicate that the liver function was seriously impaired, at least temporarily, even though pigment excretion was only slightly disturbed or may be interpreted as evidence of extensive generalized tissue breakdown. The absence of tyrosine in the urine argues against liver autolysis (42). The absence of liver necrosis or evidence of recent repair or regeneration at necropsy is further support for this point of view. The traces of cholesterol ester in the blood in the early part of the disease points, however, to liver damage (20).

The chronic cholangitis may be the most significant pathological feature in the liver. This has repeatedly been found in the cases in which renal failure followed cholecystectomy. Such cases have been reported by Hoesch, Devay, Fuentes and Rubino, Merklen, Bicart and Adnot, and others.

Group 3. Cases with neoplasm of the liver or biliary passages developing anuria and azotemia have been cited by Frerichs, Gilbert, Chabrol and Benard, Koch, Hess, Schutz, Helwig and Kuhn.

Group 4. Cases of apiol poisoning with azotemia and jaundice have been reported in the French literature. Cases with general infections due to gram-positive cocci, i.e. pneumococci, streptococci, and staphylococci, with hepatic insufficiency and anuria have been recorded (Quenu and Joltrain, two cases, 1909; Widal and Abrami, one case, 1908; Rousel and de Lavergne, five cases, 1919;



Fig. 1. Acute Necrotizing Arteritis With Thrombosis in the Liver. Illustration from a case of subacute glomerulonephritis with necrotizing arteritis of the liver and pancreas and jaundice. (Clinical Pathological Conference Case Report, J. Mount Sinai Hospital, 2:286, 1936).

Savy and Thiers, one case, 1929; Lederer, one case, 1930). Hammerschlag recently reported a case of enterococcus sepsis with fever, coma, jaundice, and azotemia (150 mg. per 100 c.c. blood) with recovery.

THE ROLE OF ANATOMICAL AND FUNCTIONAL CHANGES IN THE KIDNEY IN THE DEVELOPMENT OF THE RENAL MANIFESTATIONS

Anatomical Changes. Renal lesions have been reported in connection with long standing icterus, chronic liver disease without jaundice, and in circumstances where acute infections in the biliary tract or trauma to the liver substance occur. The pathological findings as a rule do not correspond to the severity of the clinical picture.

The renal lesions dependent on jaundice have adequately been described as a "bile nephrosis" by Moebius, Fahr and Wilbur. The integrity of the glomerulus under this circumstance has been emphasized.

Renal lesions have been described in acute yellow atrophy of the liver by Frerichs, Minkowski, Kraus, Versé, Hauser. More recently, Mayer, and also Koch, have made extensive observations. The picture has been characterized as a nephro-dystrophy with fatty changes in the tubules, mainly the convoluted tubules. Rarely, the picture assumes the appearance of a necrotizing nephrosis (Our Case No. 1; Bompiani).

The renal lesions in 12 cases of acute and subacute atrophy of the liver were studied by us. The alterations were almost exclusively confined to the tubular structures, chiefly the convoluted portions. They consisted of varying degrees of degeneration (granular, hydropic, vacuolar, and fatty) admixed with different degrees of postmortem change. Nuclei were frequently pale-staining, or absent. There were occasionally bile stained casts in the tubules and rarely bile pigment in the epithelium. Although the extent of degeneration was severe in a few cases, in none was there leucocytic infiltrations, hemorrhage or edema. The glomeruli were generally normal. No correlation could be established between the presence of azotemia and the severity of the renal lesions. Severe degenerative lesions were present in the absence of azotemia. On the other hand, a case with azotemia (urea nitrogen 40 mg. per 100 c.c.) showed no significant renal tubule change. A necrotizing nephrosis was present but once (Case 1).

Hewitt (37) analyzed 10 cases with necrosis of the renal epithelium in infections and intoxications and found that five also had lesions of the liver resembling those found in acute yellow atrophy. Helwig and Orr, and Furtwaengler reported a high-grade necrotizing nephrosis in tramuatic necrosis of the liver. Mild glomerular and also interstitial changes were also noted. In cases dying of uremia following operations on the biliary tract, tubular changes have been reported in the kidney (Clairmont and Haberer, Fitz-Hugh, Steinthal). A marked nephrosis has been reported by Schutz, Helwig and Kuhn. Fuentes and Rubino suggested the name, hepatonephrosis, to describe the renal picture in this group of cases.

The renal changes must be differentiated in the presence of jaundice as to whether they are due to the cytotoxic effects of excreted bile salts, the so-called bile nephrosis, or nephrotic changes due to other toxic factors. What relationship the renal lesions bear to the clinical renal manifestations is a matter which has not as yet been settled in other forms of renal disease. However, a lack of correlation between the severity of the renal anatomical disturbance and the clinical manifestations is definite. In traumatic liver necrosis, a direct relationship between the intensity of the liver injury and the kidney damage appears to exist.

Renal Function. The reciprocal functioning of the liver for the kidney and vice versa in physiological crises affecting either organ has been demonstrated repeatedly by the phenolsulphonthalein excretion test. If one path of excretion becomes blocked, the other compensates and excretes the dye.

The specific gravity of the urine is usually normal in the presence of disease of the liver and gall bladder with or without jaundice. The concentrating power of the kidney is maintained, usually even in patients with oliguria and azotemia. Meczner (46) combined Volhard and galactose tolerance tests in 19 patients with liver disease. The specific gravity of the urine remained normal despite impairment in liver function and oliguria.

Occasionally, isosthenuria is present. In our Case No. 2 there was persistent isosthenuria despite diure-

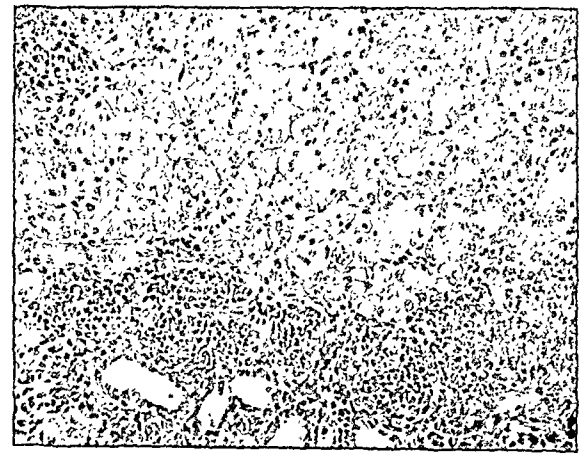


Fig. 2A. Photomicrographs. Biopsy of Kidney. Subacute Yellow Atrophy of Liver with Anuria (Case 1). Severe Tubular Degeneration with Regeneration. Acute Inflammation of the Stroma.

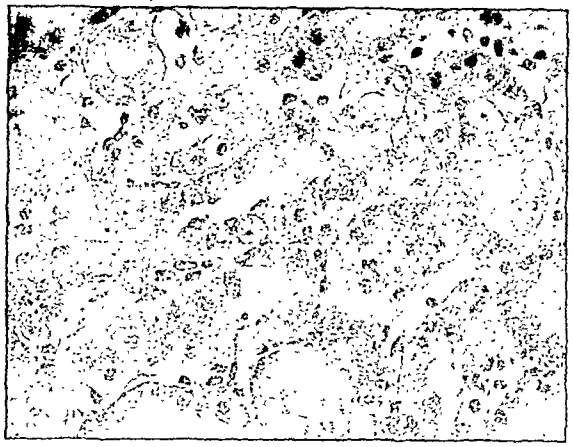


Fig. 2B. Degenerative nephrosis; higher magnification than Fig. 2A.

sis and relief from jaundice. A renal morphological basis was not demonstrable at necropsy. Koch observed isosthenuria in two cases of carcinoma of the liver with oliguria. In Weil's disease he found isosthenuria commonly, although urea clearance was normal. In acute yellow atrophy of the liver, however, he and also Hess found no deviation from the normal in the specific gravity of the urine. This has also been our experience. The renal functional disturbances when they occur appear not to be directly related to anatomical changes in the kidney.

THE REGULATION OF WATER AND ION EQUILIBRIUM BY THE LIVER

WATER ECONOMY

Numerous claims have been made that the liver is responsible in great measure for the water balance in the organism (2, 3, 4). The liver may act as a reservoir for water (49). By regulation of the minerals and chemical reaction of the blood the liver may assist in water transport. Furthermore, hormonal properties accredited to liver tissue may influence diuresis (49). The liver is concerned with the synthesis of blood proteins. Deficiency of blood proteins leads to colloid osmotic pressure changes which may cause water to leave the blood. Water tolerance tests in liver disease indicate a tendency to water retention (2, 3, 9, 10, 46).

Mineral Metabolism. It has been asserted that the liver regulates the ionic equilibrium of the body. A direct action of specific ions on liver cells has been claimed (3).

Beckmann (8) has made extensive observations on the influence of various ions injected into the portal vein. The passage of the respective ions through the liver effected changes in the water concentration of the blood. With experimental bile duct obstruction the influence of individual mineral elements was retained, whereas with liver damage the specific effect was lost and water entered the blood directly. The intact liver is necessary for this ionic equilibrium. Beckmann further studied the effect of injury of various components of liver tissue, i.e. biliary tract, parenchyma, reticulo-endothelial system, upon mineral metabolism. Only in parenchymal damage did he observe water metabolism disturbance, evidenced by prolonged and increased escape of water from the liver into the blood.

Disturbances in blood and urinary chlorides have been noted. Chloride retention has been claimed in cirrhosis of the liver and liver atrophy (40). Kahn and Barsky reported an increase in sodium and chloride in the chemical analysis of the liver in a case of acute yellow atrophy.

Sodium retention has been demonstrated in catarrhal jaundice (56). A disturbance in the inorganic salts of the blood and tissues in hepatic disease has been reported (55).

Considering the intimate roles that the liver plays in the transport of water and storage and distribution of certain ions it may be conceived that disturbances in these functions may lead to a retention of fluids and ions in the tissues. Renal manifestations may thus arise entirely on an extrarenal basis through prerenal deviation of fluids, i.e. the water is not available for excretion by the kidney.

COMMENT

Disorders occur with combined disease or functional disturbance in the liver, biliary tract and the kidney. It is clinically important to recognize whether both these organs are affected by the same etiological agent or whether either organ had previously been diseased by a chronic process. These distinctions form the basis for classification.

The label "hepatorenal syndrome" has been applied to cases of liver or gall bladder disease complicated by renal failure. First recognized by the surgeon, procedures on the biliary tract were linked with the ensuing renal events. Anesthesia, accidental ligation of an anomalous vessel, traumatic necrosis of the liver, infection in the gall bladder bed, or decompression of the biliary tract in obstructive jaundice were some of the factors incriminated. Experimental investigation was directed along these channels.

Renal lesions, essentially nephrotic in character have been produced experimentally and described clinically. They have been ascribed to specific nephrotoxins liberated from necrotic liver tissue, to vasospastic substances derived from the same source effecting spasms of the renal vessels with ischemia and necrosis of the renal epithelium, and also to nonspecific toxic effects upon renal epithelium in its physiological activity in eliminating toxic substances from the body, mainly through the convoluted tubules (36, 13).

From our own experiences and from a review of many cases in the literature it is evident that the renal changes are not constant and appear to bear no constant relationship to the severity of the clinical picture. A functional change is demonstrable in some cases as evidenced by isosthenuria.

Similar renal changes and renal functional disorganization have also been noted in ileus, intestinal intoxication of infants, and diabetic acidosis. These conditions may also be characterized by renal failure. In these conditions, the renal anatomical lesions are interpreted to play only secondary roles. The primary factor is accepted to be extra-renal.

Unfortunately, the analogy between these conditions and those belonging to the so-called "hepatorenal syndrome" has been ignored, mainly because chronologically a surgical procedure may have preceded the renal failure. However, we have observed that the

classical features may occur in cases without trauma, operation, anesthesia, or decompression of an obstructed biliary tract. Jaundice and its concomitant features need not participate.

Renal failure has occurred where vomiting was minimal, where no hypochloremia existed and where the fluid intake has been adequate as in our second case.

In ileus, diabetic acidosis, and intestinal intoxication of infants, a definite intoxication exists. Loss of water, chlorides, base, and a disturbance in acid-base equilibrium have been demonstrated. In the present group of cases, chemical findings in the blood, aside from azotemia and creatinin retention, have as yet indicated no special type of change.

Profound disturbances in water and mineral metabolism may occur with liver damage. Water, sodium, and chloride, appear to be retained, especially in liver tissue. Knowledge of the complete electrolyte pattern of blood and tissues awaits investigation of the distribution of extracellular and intracellular water and minerals. It is our belief that the results of such studies will adequately explain the mechanism of the pre-renal deviation of fluids in the cases belonging to the so-called hepatorenal syndrome. An infection or intoxication, probably, disturbs the function of the liver in regulation of water and minerals, initially. The renal lesions are caused by this same factor, primarily, or possibly by the chemical changes brought about by the prerenal deviation of fluids.

There is no evidence for the existence of a specific relationship between the disturbance in the liver and the renal manifestations. The use of the term, "hepatorenal syndrome" should therefore be discouraged.

SUMMARY

Clinical disorders in which infection or intoxication involves the liver and kidney in the same pathological process have been distinguished from those in which liver damage or biliary tract infection antedates renal manifestations. A point has been made of recognizing the significance of acute disease of either the liver or kidney when it supervenes upon chronic disease of the other organ.

The renal manifestations which may occur in the course of degenerative disease of the liver, biliary tract infections, malignancy of the liver and bile passages, trauma to the liver or following surgical procedures upon the biliary tract are ascribed by us to abnormal extra-renal conditions due to hepatic dysfunction. The liver functions concerned with the regulation of water and mineral balance are markedly disturbed. Anuria and azotemia, under these conditions, result from pre-renal deviation of fluids. Water is not available for renal excretion. Surgical procedures, jaundice, shock, decompression of an obstructed biliary tract and vomiting are not essential factors in producing the renal manifestations in this group of cases.

The nephrotic lesions which have been found in some of these cases, occur inconstantly and do not determine the clinical renal manifestations. They are rather an indication of a profound intoxication or they may be caused by disturbed extra-renal conditions.

Analogous renal manifestations occur in other clinical disorders, i.e. diabetic acidosis, ileus, and intestinal intoxications of infants, and are associated with known chemical changes in the blood and tissues. No specific relationship between liver damage or infection in the biliary tract and the renal manifestations has been demonstrated. The underlying chemical nature of this intoxication and its effects is unknown. The use of the clinical label, "hepatorenal syndrome" is to be avoided.

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Physiological and Clinical Study of Patients After Subtotal Gastrectomy*†

By

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IN an earlier paper we have described a technic for and the results of subtotal gastrectomy (s.g.) for duodenal and gastric ulcer (1). In the five years following this publication a number of patients have been studied in detail in the Department of Gastro-Intestinal Physiology, founded since then. The present paper deals with the size of the postoperative stomach, emptying time (E.T.), hunger contractions (H.C.), direct observations of the mucosa by gastroscopy, secretion and blood findings, and clinical end results of patients following subtotal gastric resection. For obvious reasons not all of the tests could be performed on every patient and at the same date. An attempt is made to interpret subjective symptoms with the changes in gastric physiology. Forty-four ulcer patients were selected at random from the gastro-intestinal clinic of Michael Reese Hospital; all were white, 36 males and 8 females. The age (at time of operation) varied from 21 to 54 with an average of 39 years. Nine of the patients had been operated on previously at other institutions, a gastro-enterostomy or pyloroplasty having been performed. The final diagnosis of the 44 cases were—30 duodenal ulcer (D.U.), 5 gastric ulcer (G.U.), 3 gastric and duodenal ulcer, 6 gastrojejunal ulcer (G.J.U.). One patient diagnosed with gastric ulcer also had a gastro-enterostomy and ulcer of the stomach occurred just above the stoma (No. 32). One patient with a gastrojejunal ulcer also had a recurrence of his duodenal ulcer (No. 36).

RESULTS

1. Emptying Time and Size of Stomach. Method: Using a milk barium mixture the emptying time was determined by fluoroscopy before and after operation. In some cases repeated examinations were done. The normal average emptying time by our method is from 3½ to 4½ hours in the intact stomach. An estimation of the size of the stump was made from the X-ray film in the post-operative examination. The average period of time after operation was 3 years (2 weeks to 14 years). It is evident that the E.T. was diminished very considerably in most patients; in some of them emptying times as short as 15 and 20 minutes are recorded, whereas before operation the values were 270 and 330 minutes respectively (Nos. 13 and 28). In other instances subtotal gastrectomy produced little or no change in E.T., as seen in No. 5 (60 and 80 minutes, G.E.), in No. 10 (270 and 240+ minutes), and in No. 18 (240+++ and 240+++ minutes, G.E.).

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The complete tables of this paper can be obtained from Dr. H. Necheles, Department of Gastro-Intestinal Physiology, Michael Reese Hospital.

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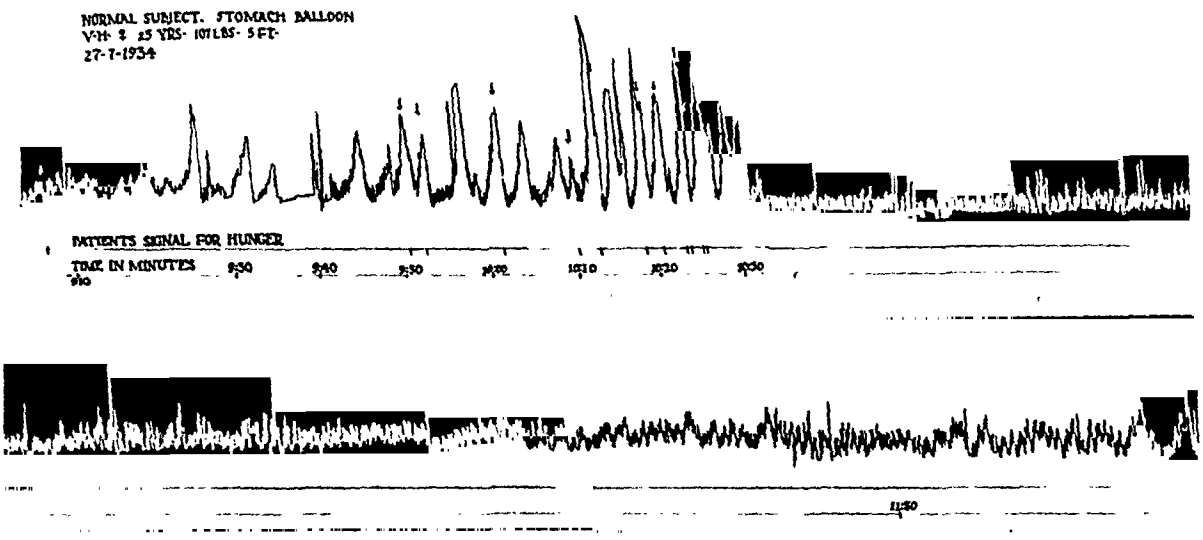


Fig. 1

Fast emptying of the resected stomach may persist for many years (No. 13, E.T. 15 minutes, six years after operation, also Nos. 1, 21, 23, 28 and 35). In the course of time, in some patients the E.T. changes while in others it remains remarkably constant. Moreover, some patients showed a decreasing emptying time, whereas others showed the reverse. In this connection it ought to be mentioned that in some patients the size of the stump of the remaining stomach increases as time progresses (Nos. 9, 10, 17, 34, 36 and 42). This is similar to what occurs in dogs after wide resection of their stomachs, and it may influence E.T. It may also explain why patients immediately after operation can eat only small meals, but are able to increase the size of the meals as time goes on. In a few cases the size of the stump diminishes gradually (Nos. 1 and 4). It is puzzling, that such short E.T. as 15-30 minutes did not produce clinical symptoms except possibly in one case (No. 13). Distention of the duodenum produces pain and nausea. It may either be that the liquid barium meal is not an adequate functional test, or that in these patients no backflow into the proximal loop of the gastro-enterostomy occurs. Dr. R. Schindler*, believes that gastrectomies are followed by good results clinically, if they function like the pyloric sphincter, and in two of our patients he observed such action and demonstrated it to some of us, (Nos. 5 and 6). The E.T. in these two instances were 80 and 60 minutes respectively, which is considered as normal in a subtotal gastric resection. In these two patients a normal mucosa of the stomach was reported and the clinical end result was considered to be satisfactory.

A comparison between E.T. and postoperative results fails to reveal consistent relationship between satisfactory clinical results and longer or shorter E.T. The E.T. in the patients called clinically satisfactory varied between 20 and + 240 minutes with an average of 92 minutes (29 cases). One patient with occasional epigastric distress (No. 9) had an E.T. of 95 minutes, and the unsatisfactory patients (Nos. 13, 36, 38 and 39) had E.T.'s of 15, 105, 60 and 75 minutes respectively.

Comparison between size of the stump of the stomach and E.T. reveals a possible relationship. Five patients with 1/5-1/4 of the stomach left, had an average E.T. of 72 minutes, 20 patients with 1/3 of the stomach left, had an average E.T. of 91 minutes and 4 patients with 1/2-2/3 of the stomach left, had an average E.T. of 80 minutes. A comparison between the size of the stump of the postoperative stomach and clinical end results fails to produce evidence of relationship. Patients with satisfactory clinical results (24 cases) had an average stump of 34% (25%-66%); unsatisfactory clinical results had an average stump of 31% (25%-33%, 4 patients); and one patient with occasional epigastric distress had a stump of 50% (i.e. half the size of the original stomach).

TYPE OF HUNGER CONTRACTIONS

Methods: Gastric motility in the fasting state (12-14 hours p.c.) was studied and recorded by the balloon-manometer method described by Carlson (2). The tests lasted from 2 to 4-1/2 hours. In the following discussion Type I denotes tonus waves, Type II denotes hunger contractions and Type III denotes hunger contractions of tetanic type. The regularity of periodic recurrence of rest and activity and the number and height of hunger contractions was considered also. Figure 1, representing the periods of hunger and rest of the stomach of a normal student, illustrates the normal occurrence of Type I, II and III.

Thirty-one motility tests were performed on 23 patients at an average interval of one year between operation and test (2 weeks to 4 years and 4 months). In three patients studies were made before and after operation, in two before operation, only, and in 18 after operation only. In those in whom the tests were repeated at varying intervals after operation, identical results were obtained. Thus, repeated motility tests were performed in patient No. 2, 11 months, 11 1/2 months, and 12 1/2 months after operation. In patient No. 3, 11 and 16 months, and in patient No. 34, 1 1/2 months and 1 year after operation.

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RESULTS

In the motility tests there was no normal variation between periods of hunger motility and rest, as exemplified in Figure 1. In 2 patients (Nos. 32 and 34) practically only tonus waves were recorded, while in the rest of the tests continuous motility was observed with very short and irregular periods of rest intervening. By irregular we refer to deviations from the typical course of a period of hunger contractions, as described by Carlson (2) and as partly exemplified in Figure 1.

Figure 2 shows one such test done six months after operation on patient No. 28. In this, as well as in some other cases, the contractions appeared to be more of the intestinal than of the gastric type. We are certain, however, that the balloon was in the stomach. In the three patients observed before and after subtotal gastric resection practically the same type of motility was found in both instances. In only one patient was tetanus observed (No. 4).

The patients registered (electric signal) Type II and III contractions as hunger pangs although they did not signal at every such contraction. No significant change in the frequency of hunger pangs was noted in the three persons before and after operation.

In 18 patients (not tabulated) of whom we thought that subtotal gastrectomy would be performed sooner or later, motility tests were recorded. All of them had an established diagnosis of duodenal ulcer. Seventeen were male, 1 female. Normal periodicity was observed in only two persons; atonia obtained in two tests; in one of these severe epigastric pain developed. Irregular periodicity occurred in six tests. In 8 tests constant activity prevailed. Type III contractions were not observed in this series.

Figure 3 represents a tracing from one of the ulcer patients with continuous gastric motility.

GASTROSCOPIC FINDINGS

Seventeen patients were gastroscoped by Dr. R. Schindler. The gastroscopic visualization of gastrojejunal ulcer was verified by X-ray examination and by the clinical history in one instance (No. 36). A normal mucosa was reported in four patients, while in remaining patients gastritis or erosions were observed. In two instances a pylorus-like functioning of the gastrojejunal stoma was reported.

GASTRIC ANALYSIS

Methods: Histamine tests were done as described by us in a previous paper (3), 0.35 mg. of histamine acid phosphate being injected subcutaneously. In the case of postoperative tests the stomach contents were aspirated through a Levin tube with constant suction, and each small sample tested separately for free acid, as also described previously (4). The latter method is important in cases of subtotal gastric resection, because it detects free acid, where other methods frequently fail. The Ewald meal employed was identical in character and technic with that described by Vanzant, Alvarez, Eusterman, Dunn and Berkson (5). In three tests alcohol was used as secretagogue, 100 c.c. of a 7% solution being employed. Forty-six histamine and 20 Ewald tests were made. On a number of patients more than one test was performed, but only the last one made (i.e. longest period since operation) is being reported. In a number of patients Ewald tests were made before operation and Histamine tests after operation.

Results: It is not surprising that after subtotal gastrectomy large residual contents of the fasting stomach would be absent (Nos. 29 and 31), and that little residue is found in all cases. The degree of acidity of the fasting secretion (basal) of the stomach is of importance, since we find it high in a great number of cases with duodenal ulcer. It probably is due to the high nocturnal acid secretion in duodenal ulcer patients as described by Sippy, Rehfuss and Hawk, Winkelstein, Palmer and others (6). In the case of the partly resected stomach, the free acidity of its residual contents either diminishes considerably or drops to zero. This occurred in 11 cases while in Nos. 16, 28, 29 and 36 the free acidity was either higher than before operation, or not appreciably diminished. Following a stimulus (histamine in most tests), the acid secretion was higher in 2 patients than before operation (No. 18 and 36) in 4 patients no significant change took place, the acid secretion remaining high (Nos. 2, 3, 4, 16), in 7 there was a considerable reduction in free acidity (of 50% and more), and in 18 patients no free acidity was found. This means that of 31 patients observed, 25 showed either greatly reduced or no free acid secretion to a secretory stimulus after subtotal gastrectomy. Repeated

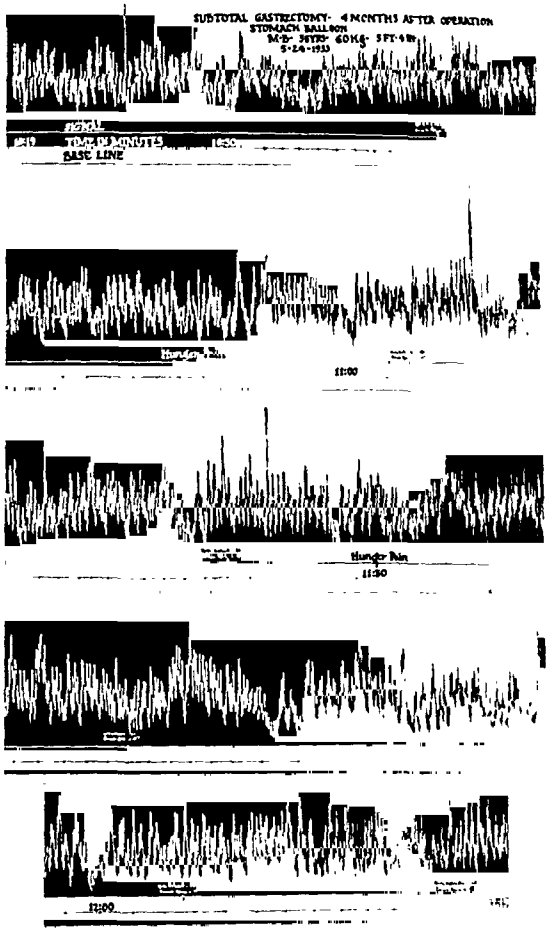


Fig. 2

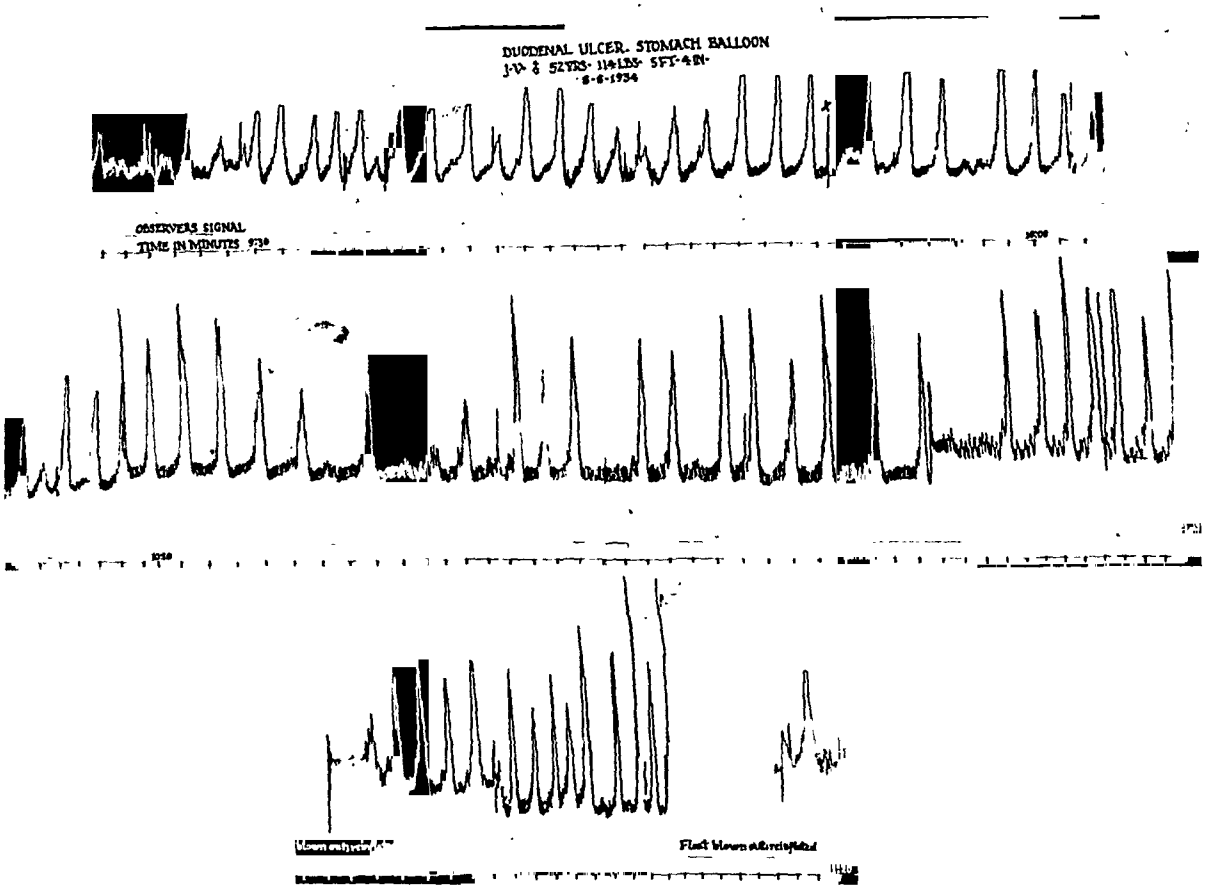


Fig. 3

tests of stomach secretion following histamine were performed on 10 patients, with intervals of from 1 to 48 months after operation. Constant suction and fractional testing of small samples were done in every case (4). In nine out of 10 patients free acid disappeared after operation. In one patient the acidity stayed high (No. 4), and in 2 patients a moderate degree of free acidity returned 2 years and 1 year after operation (Nos. 2 and 44). In another patient the acidity of the residual contents of the stomach (see above) was increased considerably 8 months after operation, while the response to histamine remained low. This is important, because residual acidity probably is closely related to night secretion, which has been reported to be high in patients with duodenal ulcer (see above). It is of interest therefore, that high acidity of residual contents returned 8 months after operation, and that considerable free acidity following histamine stimulation was found 1 and 2 years after operation.

BLOOD PICTURE

In the following discussion blood findings are considered satisfactory when the red blood count was above 4,000,000 and hemoglobin above 70%; below these marks the patient is designated anemic. Of 28 patients observed before, and later than 6 months after operation, 6 had distinct anemia after operation. (Nos. 15, 18, 28, 30, 31 and 41). Three showed no considerable change of their red cell count and hemoglobin, 12 had definite improvement of one or both, and in 9 a decrease of red cell count and hemoglobin or both took place, but no anemia occurred. It is difficult to evaluate these findings, because we are not certain whether all of the patients conscientiously took the iron compounds given to them. No case of pernicious anemia was found. No eosinophilia occurred in this group as one might expect if the theory of vagotonia and resultant frequent eosinophilia were true. In a number of patients the monocyte count seemed somewhat high and in a number of patients the lymphocyte count changed after operation, in most cases showing an increase. But these changes seem to be too small to invite speculation.

CLINICAL END RESULTS

As "Clinical end results" the opinion of the Internist is presented, with due consideration of the opinion of the patients. In the majority of the cases the opinions of physician and patient are in accord, but in a few, in which distinct psychoneurotic traits were apparent, and in which complaints of the patient seemed to be without reasonable basis only the opinion of the physician is given. "Satisfactory" means no complaints and ability to work; "unsatisfactory" denotes complaints and inability to work; occasional epigastric distress (in No. 9) denotes unquestionable improvement from a previous state of more or less constant epigastric distress; yet the treating Inter-

nist is not quite satisfied with the condition of the patient; due to dietary indiscretion or alcoholism, occasional gastric distress of slight nature sometimes appears.

Forty-four patients have been followed closely enough to be included in the following discussion. Of these, 37 present satisfactory end results (group A), 2 have occasional epigastric distress (group B) and 5 are classed as unsatisfactory (Group C), of this latter group only one is diagnosed as gastrojejunal ulcer (No. 36). What findings have group A, B, and C, in common?

(1) *Body weight:* In 22 patients gains are recorded after operation. Increase in body weight occurred only in persons classed as "satisfactory clinical end results." In 6 patients distinct loss of weight occurred (below 2 kg.). Three of these are classed as satisfactory (one of them being psychoneurotic), one as occasional epigastric distress, and 3 as unsatisfactory, one of them being diagnosed as gastrojejunal ulcer.

(2) *Emptying Time of Stomach:* Thirty-five observations on clinical end results and emptying time are recorded. Of these 7 had a short E.T. of 15-30 minutes, while the rest of the 28 had an E.T. from 30 to +240 minutes. The group with short E.T. contains 5 satisfactory end results and 2 unsatisfactory end results. The group with longer E.T. contains 24 satisfactory and 3 unsatisfactory end results, and one patient with occasional epigastric distress.

(3) *Hunger Motility of the Stomach:* Hunger motility of the stomach was irregular in all of the 19 patients studied. Of these 18 presented "satisfactory clinical end results" and one "unsatisfactory clinical end results."

(4) *Size of Postoperative Stomach:* Of 29 observations 20 showed 1/3 (a), i.e. the approximate size of stomach soon after operation. Five showed 1/4 to 1/5 (b), i.e. a decrease of size of stomach after operation, and 4 showed 1/2 (c) to 2/3, i.e. increased size of stomach after operation. Group (a) contained 17 cases of satisfactory and 3 cases of unsatisfactory end results. Group (b) had 4 satisfactory and one unsatisfactory end results; the unsatisfactory case had the smallest stomach observed in the group (1/5, No. 38). Of Group (c), 3 cases are satisfactory end results and one has occasional epigastric distress.

(5) *Gastroscopy:* Of the 17 cases included in this group, four appeared normal and 13 presented pathologic appearance. All of the normal cases are grouped as satisfactory end results. Of the second group 10 are satisfactory end results, one patient has occasional epigastric distress and 2 are considered unsatisfactory end results.

(6) *Gastric Analysis:* Of 37 patients end results are classified as satisfactory in 31 and in 4 as unsatisfactory, while 2 had occasional epigastric distress. The group of 31 satisfactory end results contains 8 patients with moderate amounts of free acid after stimulation, 3 patients with high acid response and 20 with low response or anacidity. The second group (unsatisfactory end results) contains one patient with a high acid response (G.J.U.) and 3 with low acid or anacidity. One patient of the group with occasional epigastric distress has anacidity, the other a moderate degree of acidity.

(7) *Blood:* Of 30 patients 24 blood findings are classified as satisfactory (a) and 6 as anemia (b). Group (a) contains 19 satisfactory and 4 unsatisfactory clinical end results, and one patient with occasional epigastric distress. All six patients of group (b) (anemia) are classed as satisfactory clinical end results.

DISCUSSION AND CONCLUSIONS

It appears that gain or loss of body weight follows the clinical end results. Only one patient classified as a satisfactory end result lost considerably in weight but this patient is a psychoneurotic (No. 8). All the remaining "satisfactory end results," had small losses of weight, remained stationary or gained weight. One patient with occasional epigastric pain lost 2.5 kg. (No. 9), one with gastrojejunal ulcer lost 3.8 kg. (No. 36) while the "unsatisfactory end results" lost 7 and 4 kg. (Nos. 13 and 43 respectively). Therefore it seems indicated to follow body weights of such patients as indicator of clinical improvement.

In analysing the emptying time of the postoperative stomach it appears that slower emptying time offers better clinical end results than rapid emptying time.

No correlation can be found between hunger motility and clinical end results. It is concluded tentatively that although in practically all cases with irregular hunger motility satisfactory clinical end results were found, yet a functional irregularity present before operation remains. No correlation between clinical end results, and size of gastric stump could be detected. The difficulty of estimating gastric size by X-ray makes the size of the stump a questionable value in determining end results of subtotal gastrectomy.

No correlation can be seen between gastroscopic findings and clinical end results, even after grouping the gastric findings into moderate and severe pathology of the gastric mucosa (Nos. 1, 8 and 42). One case of G.J.U. apparently was diagnosed as such.

Analysis of gastric secretion shows that no correlation exists in this clinical group between high or low free acidity and clinical end results. In the group with satisfactory clinical end results the greatest incidence of high acid response was found. The patient with gastrojejunal ulcer had a high free acid in the unstimulated and stimulated stomach, but the other unsatisfactory end results, including the patient with occasional epigastric distress have moderate or low acid response or anacidity.

Studies of the red blood count and hemoglobin show a negative correlation with clinical end results. Normal blood findings occurred in the unsatisfactory clinical end results, and all 6 cases of anemia appeared as satisfactory clinical end results.

Von Haberer's clinic (7) reports as a striking feature after gastric resections the absence of motor disturbance and of abnormal roentgenological signs on the one hand and the frequent subjective complaints on the other, and a fairly rapid emptying, but no dumping. The same was reported in more detail recently (8). Raydin and his co-workers using different test meals conclude that the mechanism by which the postoperative stomach empties itself is similar to the normal stomach with the pylorus intact, and that it does not depend on the size of the stoma (17). Wilensky and Crohn (9) report that following partial gastrectomy in only a minority of cases does the stomach return to an almost normal state of functional activity (balloon method). The same was reported by Rogers

(10), but he did not find regular hunger pangs associated with hunger contractions in his patient. Shapiro and Berg (11) and Fauley, Strauss and Ivy (12) report the effects of subtotal gastrectomy on dogs; acid secretion gradually returned to its original level. Walters (13) reports that relative achlorhydria does not occur in all cases of subtotal gastric resection in man. We have to consider, however, the gastric pathology before operation, as well as the occurrence of gastritis after operation, which will modify the gastric acid response to a stimulus. Therefore it would be desirable to gastroscope a group of patients a number of times before and after subtotal gastrectomy. Lewison and Ginsberg (14) in a previous paper observed permanent achlorhydria in the majority of their cases, but Klein (15) found a higher incidence of acid secretion in a similar group of patients. In a recent paper Milanes (16) reports hypermotility and a great incidence of histamine refractory achlorhydria after subtotal gastric resection. It is not possible to review the entire literature, but the above quotations and our own findings give evidence of the many contradictions in most of the functional problems involved in subtotal gastrectomy. In addition one must bear in mind not only the different methods of resection, but also the variations in each of them, not only modifications, but also slight and perhaps unconscious variations from case to case in the hands of the same skilled operator. Individual conditions and postoperative changes (like adhesions) probably make the outcome of each case somewhat different. To the great number of physical factors must also be added the various psychic ones and the importance of the sociological background (including nutrition) of the individual patients. The frequent subjective complaints, in our experience are present during the first six months after operation. In those patients who have definite social or economical conflicts either antedating or following the operation the subjective complaints continue for a long period and do not disappear. Perhaps they only disappear after proper social adjustment and medical therapy.

SUMMARY

In a group of 44 patients the body weight, emptying time, size, motility and secretion of the stomach, its mucosa by gastroscopy, and the erythrocyte and differential count and hemoglobin was studied. The body weight seemed to be a fairly good indicator of postoperative results after subtotal gastric resection. The results of all functional tests and observations performed varied too much to be considered as reliable indicators of clinical end results.

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The Pathogenicity of Four Strains of Endamoeba Histolytica from Chicago*

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ON March 14, 1934, we received from the Department of Health of Chicago, Illinois, four strains of *Endamoeba histolytica* which had been obtained from persons in that city. Previous to this time we had been studying the pathogenicity of various strains of *E. histolytica* for kittens (1). Five strains from Tennessee had been studied and it had been found that two of these, obtained from a community in the hill region of Middle Tennessee, produced a lower incidence of infection than the other three strains obtained from a community in the bottom-land of West

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Tennessee. In the hill community 38 per cent of the inhabitants had been found to harbor *E. histolytica*, but there was no evidence of occurrence of acute amoebic dysentery, whereas in the bottom-land community only 19 per cent of the inhabitants had been found to harbor *E. histolytica*, but twenty-five cases of acute amoebic dysentery had occurred during the past two and a half years.

TABLE 1

Pathogenic indices of four strains of E. histolytica from Tennessee repeatedly tested in kittens

Average number of days since isolation of culture	Number of kittens inoculated	Kittens developing infection		Pathogenic index
		Number	Per cent	
Strain A-1 (Hill Country)				
220	38	12	31.6	0.58
600	20	4	20.0	0.54
957	21	8	38.0	0.57
1023	24	7	29.2	0.53
1053	20	6	30.0	0.58
1329	25	8	32.0	0.50
1774	20	5	25.0	0.57
Strain A-2 (Hill Country)				
222	19	15	79.0	0.49
600	20	5	25.0	0.69
958	22	7	31.8	0.65
1082	21	8	38.1	0.58
1328	23	7	30.4	0.67
Strain B-1 (Bottom-land)				
180	20	12	60.0	1.06
602	20	11	55.0	1.01
875	25	16	64.0	1.09
1036	24	20	83.3	1.25
1047	20	13	65.0	1.28
1279	24	12	50.0	1.05
1745	29	20	69.0	1.19
Strain B-2 (Bottom-land)				
186	20	13	65.0	1.15
612	11	5	45.0	1.35
1071	20	12	60.0	1.31
1320	20	11	55.0	1.32

In the performance of the above experiments we kept all strains of the amoebae in culture on similar media consisting of an egg-Ringer base overlaid with horse serum-Ringer (1-6) with the addition of sterile rice flour. Kittens were inoculated by direct injection into the ileum following laparotomy, and twenty or more kittens, usually weighing between 200 and 600 grams, were inoculated in each experiment. The pathogenic activity of each strain of amoebae was determined by classifying the colons of successfully infected kittens at autopsy into nine classes according to the extent and severity of the lesions. Since time was an important element in the development of lesions, the number of days each kitten survived after inoculation was recorded and the "pathology produced per day" was calculated by dividing the number of the class to which each colon was assigned by the number of days of survival after inoculation. The average of these quotients for a series of twenty or more kittens was designated the "pathogenic index" of the strain of *E. histolytica* employed (2). We have tested four of the Tennessee strains at intervals over a period of nearly five years and have found that each strain has maintained a fairly constant pathogenic index. The two strains from the hill region have constantly given a low pathogenic index, whereas the two strains from the bottom-land have constantly given a high pathogenic index. The results of these experiments are presented in Table 1.

It is the purpose of this paper to record similar experiments performed with the four strains of *E. histolytica* received from Chicago. These strains are designated C-1, C-2, C-3 and C-4. They were isolated from the following cases:

Strain C-1: J. P., white male, age 26, engineer in a manufacturing plant in which a survey for *E. histolytica* was made because of water contamination. He had had no symptoms referable to amoebiasis. Cysts of *E. histolytica* were found in the stools and the organism was recovered in culture.

Strain C-2: M. B., white female, age 23, maid employed in the hotel which was the chief source of the epidemic of amoebic dysentery in 1933. There was no history of symptoms referable to amoebiasis. Cysts of *E. histolytica* were found in the stools and the organism was recovered in culture.

Strain C-3: L. L., white male, age 54, waiter employed during July, 1933, at the hotel which was the chief source of the epidemic of amoebic dysentery. Early in July he developed a bloody diarrhea and was

TABLE 2

Pathogenic indices of four strains of E. histolytica from Chicago, each tested twice in kittens

Average number of days since isolation of cultures	Number of kittens inoculated	Kittens developing infection		Pathogenic index
		Number	Per cent	
Strain C-1				
121	24	17	70.9	1.54
532	21	16	76.2	1.52
Strain C-2				
134	21	15	71.3	1.59
544	20	18	90.0	1.49
Strain C-3				
82	22	17	77.3	1.46
473	20	16	75.0	1.44
Strain C-4				
108	22	19	86.3	1.70
525	20	17	85.0	1.67

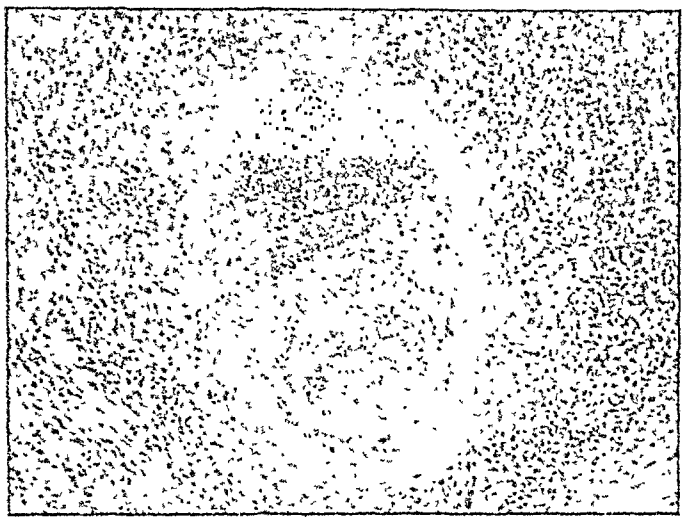


Fig. 1. Acute Necrotizing Arteritis With Thrombosis in the Liver. Illustration from a case of subacute glomerulonephritis with necrotizing arteritis of the liver and pancreas and jaundice. (Clinical Pathological Conference Case Report, J. Mount Sinai Hospital, 2:286, 1936).

Savy and Thiers, one case, 1929; Lederer, one case, 1930). Hammerschlag recently reported a case of enterococcus sepsis with fever, coma, jaundice, and azotemia (150 mg. per 100 c.c. blood) with recovery.

THE ROLE OF ANATOMICAL AND FUNCTIONAL CHANGES IN THE KIDNEY IN THE DEVELOPMENT OF THE RENAL MANIFESTATIONS

Anatomical Changes. Renal lesions have been reported in connection with long standing icterus, chronic liver disease without jaundice, and in circumstances where acute infections in the biliary tract or trauma to the liver substance occur. The pathological findings as a rule do not correspond to the severity of the clinical picture.

The renal lesions dependent on jaundice have adequately been described as a "bile nephrosis" by Moebius, Fahr and Wilbur. The integrity of the glomerulus under this circumstance has been emphasized.

Renal lesions have been described in acute yellow atrophy of the liver by Frerichs, Minkowski, Kraus, Versé, Hauser. More recently, Mayer, and also Koch, have made extensive observations. The picture has been characterized as a nephro-dystrophy with fatty changes in the tubules, mainly the convoluted tubules. Rarely, the picture assumes the appearance of a necrotizing nephrosis (Our Case No. 1; Bompiani).

The renal lesions in 12 cases of acute and subacute atrophy of the liver were studied by us. The alterations were almost exclusively confined to the tubular structures, chiefly the convoluted portions. They consisted of varying degrees of degeneration (granular, hydropic, vacuolar, and fatty) admixed with different degrees of postmortem change. Nuclei were frequently pale-staining, or absent. There were occasionally bile stained casts in the tubules and rarely bile pigment in the epithelium. Although the extent of degeneration was severe in a few cases, in none was there leucocytic infiltrations, hemorrhage or edema. The glomeruli were generally normal. No correlation could be established between the presence of azotemia and the severity of the renal lesions. Severe degenerative lesions were present in the absence of azotemia. On the other hand, a case with azotemia (urea nitrogen 40 mg. per 100 c.c.) showed no significant renal tubule change. A necrotizing nephrosis was present but once (Case 1).

Hewitt (37) analyzed 10 cases with necrosis of the renal epithelium in infections and intoxications and found that five also had lesions of the liver resembling those found in acute yellow atrophy. Helwig and Orr, and Furtwaengler reported a high-grade necrotizing nephrosis in tramuatic necrosis of the liver. Mild glomerular and also interstitial changes were also noted. In cases dying of uremia following operations on the biliary tract, tubular changes have been reported in the kidney (Clairmont and Haberer, Fitz-Hugh, Steinthal). A marked nephrosis has been reported by Schutz, Helwig and Kuhn. Fuentes and Rubino suggested the name, hepatonephrosis, to describe the renal picture in this group of cases.

The renal changes must be differentiated in the presence of jaundice as to whether they are due to the cytotoxic effects of excreted bile salts, the so-called bile nephrosis, or nephrotic changes due to other toxic factors. What relationship the renal lesions bear to the clinical renal manifestations is a matter which has not as yet been settled in other forms of renal disease. However, a lack of correlation between the severity of the renal anatomical disturbance and the clinical manifestations is definite. In traumatic liver necrosis, a direct relationship between the intensity of the liver injury and the kidney damage appears to exist.

Renal Function. The reciprocal functioning of the liver for the kidney and vice versa in physiological crises affecting either organ has been demonstrated repeatedly by the phenolsulphonthalein excretion test. If one path of excretion becomes blocked, the other compensates and excretes the dye.

The specific gravity of the urine is usually normal in the presence of disease of the liver and gall bladder with or without jaundice. The concentrating power of the kidney is maintained, usually even in patients with oliguria and azotemia. Meczner (46) combined Volhard and galactose tolerance tests in 19 patients with liver disease. The specific gravity of the urine remained normal despite impairment in liver function and oliguria.

Occasionally, isosthenuria is present. In our Case No. 2 there was persistent isosthenuria despite diure-

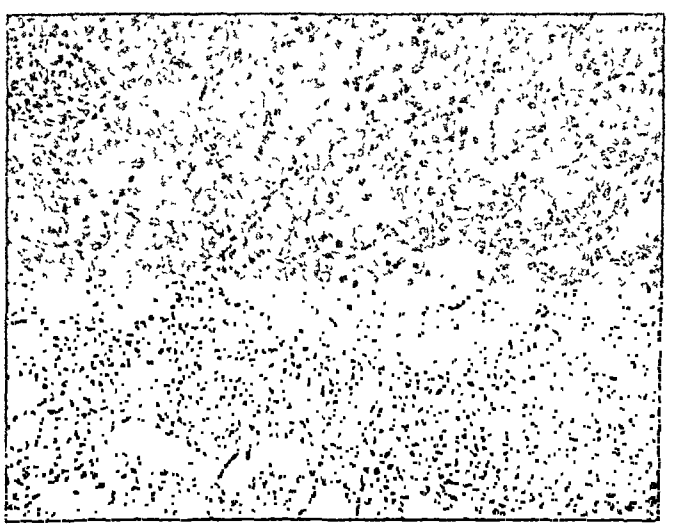


Fig. 2A. Photomicrographs. Biopsy of Kidney. Subacute Yellow Atrophy of Liver with Anuria (Case 1). Severe Tubular Degeneration with Regeneration. Acute Inflammation of the Stroma.

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The Relationship Between Oral and Gastric Bacterial Flora*

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THE relationship between the bacterial flora of the oral and gastric regions has received little attention, although considerable work has been done upon the flora in each locality. The correlation or interdependence of the two types of microbic population seems to have been given but scant consideration.

Various observers have attempted to show that certain retrogressive or degenerative oral lesions, such as pyorrhea, seeded the stomach and upper levels of the intestinal tract with pyogenic bacteria, derived from the mouth. Hurst, (1924) (1927) (1933) has called attention for many years to the importance of pyogenic foci in the mouth, throat and nose upon gastric and duodenal bacterial flora.

The present work classifies the organisms cultured from the mouth and stomach and determines the relation which these bear to each other. Effort has been made to discover the effect of continuous entrance of the exogenous flora and to study the protective mechanism by which the body defends itself against this entrance.

GENERAL TECHNIC

All experiments were performed on patients in the medical wards of the Research and Educational Hospital of the University of Illinois, College of Medicine. Although none of these persons could be considered entirely normal from a health standpoint, those exhibiting any particular dysfunction of the gastro-intestinal tract or suffering from primary anemias were not used. Cultures were made on plain agar from material aspirated from the stomach, if only the possibility of growth was to be determined. For classification, blood agar and Endo plates, as well as sugars for biochemical reactions were also used. No anaerobic cultures were made. For culturing the stomach contents one standard platinum loop of material was placed on the surface of solid media and distributed with a sterile glass spreader which was then carried to a second similar plate. To obtain cultures from the mouth, sterile swabs were rubbed across the back of the tongue, then passed twice across a sterile agar plate. With a second sterile applicator the material was spread over the surface. This swab was then carried to the second plate. By this procedure sufficient dilution was usually obtained to procure well isolated colonies.

Hydrogen ion concentration was the method used for determining the acidity of the various substances. The colorimetric method was employed using standard buffers made according to the specifications of Clark (1928). All buffers were standardized by a Leeds Northrup potentiometer. The hydrogen ion concentration gives the effective acid concentration which is the most important factor limiting bacterial growth. When control tests showed that the hydrogen ion concentration of the stomach contents was too acid to make probable the growth of organisms, varying amounts of buffered alkali made according to Clark (1928) were added. It was difficult to alkalinize the stomach. There are several possible explanations for this fact. The alkali may have passed directly through the stomach into the duodenum or it may have stimulated increased acid secretion according to Boldyreff's (1914) principle of the self-regulation of the acidity of gastric contents. The alkali was sometimes given in milk in an effort to stabilize the acid-base balance as described by Arnold and Brody (1926).

EXPERIMENTAL PROCEDURES

Experiment I: The Relation Between the Oral and Gastric Bacterial Flora. Twenty-five fasting stomachs were aspirated by means of Rehfuss tubes. Cultures were made from this material and at the same time from the mouths to determine whether or not the micro-organisms cultured from the oral cavities were similar to those found in the stomach contents as reported by Bartle and Harkins (1925) and Kopeloff (1922).

In a series of sixteen cases a preliminary procedure was carried out to determine whether there was variation in the flora in different parts of the mouth. Cultures were taken from the lips, the tip of the tongue, the back of the tongue, the gums, and from the saliva. As was also found by Arnold and Stuart (1935) there was some variation in

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classical features may occur in cases without trauma, operation, anesthesia, or decompression of an obstructed biliary tract. Jaundice and its concomitant features need not participate.

Renal failure has occurred where vomiting was minimal, where no hypochloremia existed and where the fluid intake has been adequate as in our second case.

In ileus, diabetic acidosis, and intestinal intoxication of infants, a definite intoxication exists. Loss of water, chlorides, base, and a disturbance in acid-base equilibrium have been demonstrated. In the present group of cases, chemical findings in the blood, aside from azotemia and creatinin retention, have as yet indicated no special type of change.

Profound disturbances in water and mineral metabolism may occur with liver damage. Water, sodium, and chloride, appear to be retained, especially in liver tissue. Knowledge of the complete electrolyte pattern of blood and tissues awaits investigation of the distribution of extracellular and intracellular water and minerals. It is our belief that the results of such studies will adequately explain the mechanism of the pre-renal deviation of fluids in the cases belonging to the so-called hepatorenal syndrome. An infection or intoxication, probably, disturbs the function of the liver in regulation of water and minerals, initially. The renal lesions are caused by this same factor, primarily, or possibly by the chemical changes brought about by the prerenal deviation of fluids.

There is no evidence for the existence of a specific relationship between the disturbance in the liver and the renal manifestations. The use of the term, "hepatorenal syndrome" should therefore be discouraged.

SUMMARY

Clinical disorders in which infection or intoxication involves the liver and kidney in the same pathological process have been distinguished from those in which liver damage or biliary tract infection antedates renal manifestations. A point has been made of recognizing the significance of acute disease of either the liver or kidney when it supervenes upon chronic disease of the other organ.

The renal manifestations which may occur in the course of degenerative disease of the liver, biliary tract infections, malignancy of the liver and bile passages, trauma to the liver or following surgical procedures upon the biliary tract are ascribed by us to abnormal extra-renal conditions due to hepatic dysfunction. The liver functions concerned with the regulation of water and mineral balance are markedly disturbed. Anuria and azotemia, under these conditions, result from pre-renal deviation of fluids. Water is not available for renal excretion. Surgical procedures, jaundice, shock, decompression of an obstructed biliary tract and vomiting are not essential factors in producing the renal manifestations in this group of cases.

The nephrotic lesions which have been found in some of these cases, occur inconstantly and do not determine the clinical renal manifestations. They are rather an indication of a profound intoxication or they may be caused by disturbed extra-renal conditions.

Analogous renal manifestations occur in other clinical disorders, i.e. diabetic acidosis, ileus, and intestinal intoxications of infants, and are associated with known chemical changes in the blood and tissues. No specific relationship between liver damage or infection in the biliary tract and the renal manifestations has been demonstrated. The underlying chemical nature of this intoxication and its effects is unknown. The use of the clinical label, "hepatorenal syndrome" is to be avoided.

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latter both before and after the deflection of the saliva from the stomach. This was done in the hope that the comparison of these results might determine whether or not the swallowed saliva exerted a noticeable influence on the hydrogen ion concentration and the bacterial population of the gastric contents. Although the tests were made at ten minute intervals over a two hour period no significant change could be noted in any case, either in the hydrogen ion concentration of the gastric contents or in the number of colonies in the cultures from the three sources. The results are shown in Graph III. Bell and MacAdam (1924) reported no change in the acidity of the stomach when the saliva was withheld. Kopeloff (1922) concluded from his work that the continued swallowing of saliva is the chief factor which determines the bacterial content of the stomach.

Experiment V: The Number of Organisms in the Saliva During Twenty-Four Hours.

Although the preceding series of cases showed no diminution in the number of colonies cultured from the gastric contents when the saliva was removed, it seemed advisable to culture the collected saliva and estimate the approximate number of organisms per cubic centimeter. The total amount removed during the two hour period was well mixed and dilutions were made from 1:2 up to 1:64. From a pipette which delivered fifteen drops per cubic centimeter, one drop of each of the dilutions was plated out on plain agar plates. The colonies from the culture showing best dilution were counted and the number of organisms per cubic centimeter computed. The amount of saliva per twenty-four hours calculated on the basis of the two hour observed period varied from 264 c.c. to 2280 c.c. and the estimated number of culturable bacteria for this twenty-four hour amount varied from 2,592,000 to 79,120,800. The following table gives the summary of the results.

The number of micro-organisms in the saliva secreted during twenty-four hours

Case Patient	I No. 44976	II No. 45351	III No. 45600	IV No 45677	V No. 45103
Amount of saliva in two hours	70 c.c.	163 c.c.	22 c.c.	40 c.c.	190 c.c.
Amount of saliva in twenty-four hours	840 c.c.	1956 c.c.	264 c.c.	480 c.c.	220 c.c.
Number of colonies per c.c.	6240	19,000	299,700	14,400	48,000
Number culturable bacteria per twenty-four hours	5,241,600	35,208,000	79,120,800	2,592,000	41,040,000

*Calculated on basis of two hour observed period.

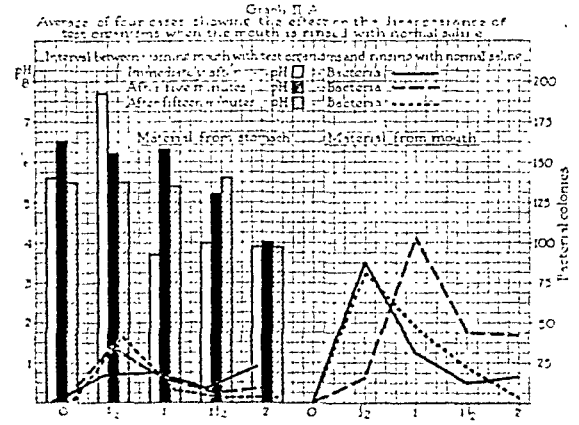
All tests were made between eight and ten a.m. before the patients had eaten breakfast. This may account for the fact that in general both the amount of saliva and the number of bacteria per cubic centimeter were less in this group of experiments than had been reported by other workers.

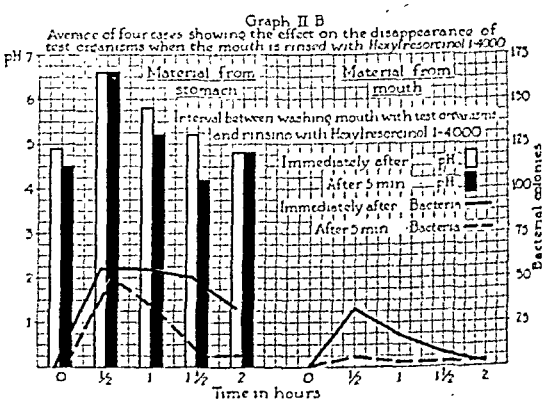
Crowley and Richet (1935), using different technic found a much higher bacterial count per cubic centimeter of saliva. Their experiment was directed toward producing growth of the maximum number of organisms, while in the present case the interest lay in comparing the growth findings from the saliva with those obtained from the gastric contents, therefore similar technic was used for both.

Hawk and Bergeim (1931) stated that the amount of saliva secreted by an adult is from 1000 to 1500 c.c. per twenty-four hours. Zaus and Fosdick (1934) reported that the basal flow of saliva averaged 0.5 c.c. per minute or 720 c.c. per twenty-four hours. During stimulation the amount increased to 2.5 c.c. per minute or 3600 c.c. per twenty-four hours. According to the counts made by Feirer and Leonard (1931) approximately 2,788,000 organisms could be grown on plain agar from 1 c.c. of fluid used as a mouth wash. They noted that there is a marked increase in organisms during the day even when no food is taken.

DISCUSSION

Cultures from the mouth and stomach show a striking similarity in bacterial flora. This must mean that the oral flora is present in the stomach either as a





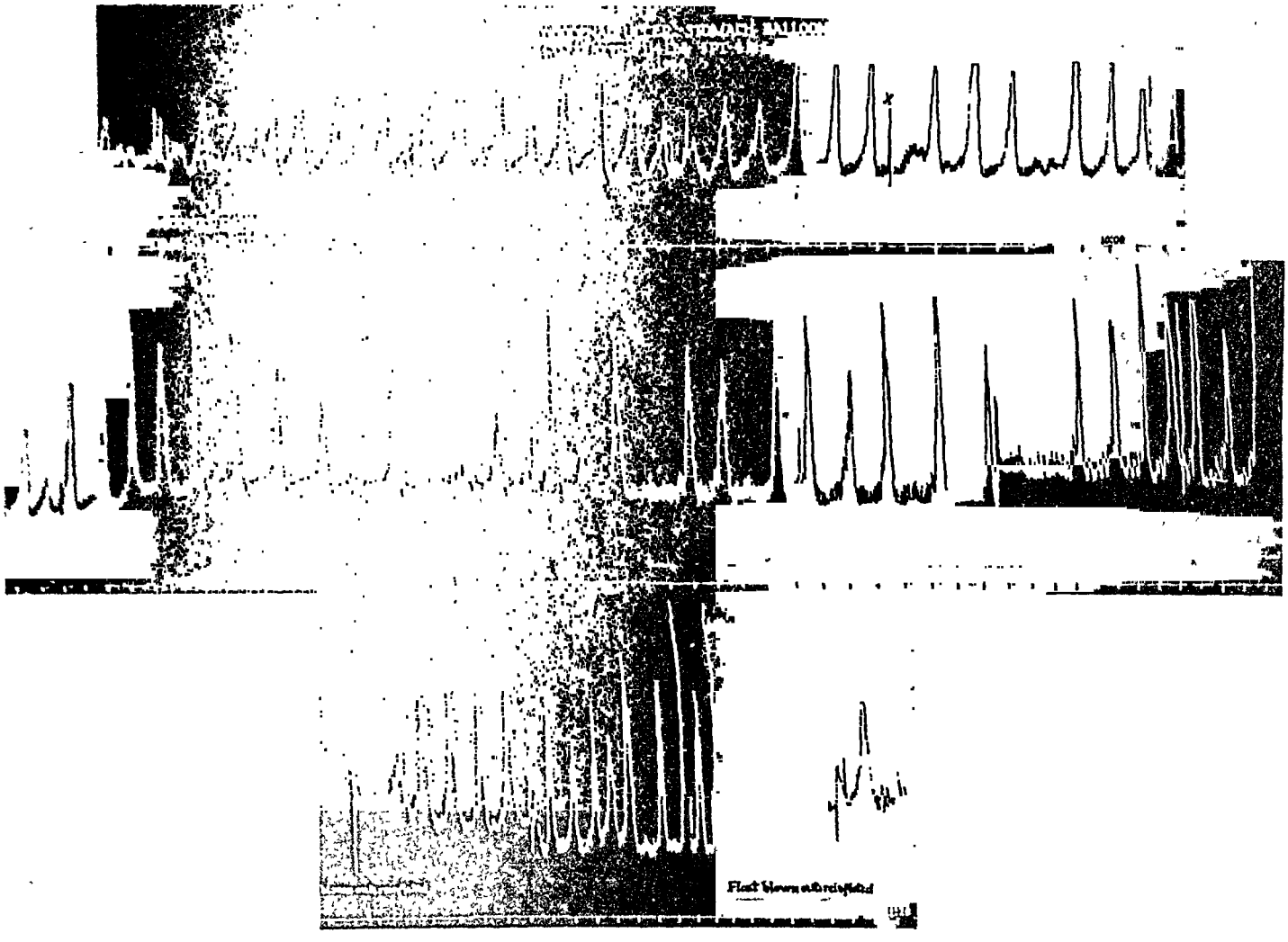


Fig. 3

tests of stomach secretion following histamine were performed on 10 patients, with intervals of from 1 to 48 months after operation. Constant suction and fractional testing of small samples were done in every case (4). In nine out of 10 patients free acid disappeared after operation. In one patient the acidity stayed high (No. 4), and in 2 patients a moderate degree of free acidity returned 2 years and 1 year after operation (Nos. 2 and 44). In another patient the acidity of the residual contents of the stomach (see above) was increased considerably 8 months after operation, while the response to histamine remained low. This is important, because residual acidity probably is closely related to night secretion, which has been reported to be high in patients with duodenal ulcer (see above). It is of interest therefore, that high acidity of residual contents returned 8 months after operation, and that considerable free acidity following histamine stimulation was found 1 and 2 years after operation.

BLOOD PICTURE

In the following discussion blood findings are considered satisfactory when the red blood count was above 4,000,000 and hemoglobin above 70%; below these marks the patient is designated anemic. Of 28 patients observed before, and later than 6 months after operation, 6 had distinct anemia after operation. (Nos. 15, 18, 28, 30, 31 and 41). Three showed no considerable change of their red cell count and hemoglobin, 12 had definite improvement of one or both, and in 9 a decrease of red cell count and hemoglobin or both took place, but no anemia occurred. It is difficult to evaluate these findings, because we are not certain whether all of the patients conscientiously took the iron compounds given to them. No case of pernicious anemia was found. No eosinophilia occurred in this group as one might expect if the theory of vagotonia and resultant frequent eosinophilia were true. In a number of patients the monocyte count seemed somewhat high and in a number of patients the lymphocyte count changed after operation, in most cases showing an increase. But these changes seem to be too small to invite speculation.

CLINICAL END RESULTS

As "Clinical end results" the opinion of the Internist is presented, with due consideration of the opinion of the patients. In the majority of the cases the opinions of physician and patient are in accord, but in a few, in which distinct psychoneurotic traits were apparent, and in which complaints of the patient seemed to be without reasonable basis only the opinion of the physician is given. "Satisfactory" means no complaints and ability to work; "unsatisfactory" denotes complaints and inability to work; occasional epigastric distress (in No. 9) denotes unquestionable improvement from a previous state of more or less constant epigastric distress; yet the treating Inter-

Atresia of the Pylorus

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IT has been computed from statistics that atresia in any portion of the gastro-intestinal tract occurs about once in every ten thousand births (1). Such anomalies, according to DeLee, occur frequently in cases of hydramnios. The case of atresia which I am reporting is one in which there was a definite gap in the continuity of the lumen of the pylorus.

CASE REPORT

History. A female baby, weighing seven pounds and three ounces was delivered after a twenty-four hour labor. Three hundred ounces of amniotic fluid were measured. The child took its feedings well but always vomited within an hour. The stools during the first four days after delivery consisted of a small amount of meconium.

Examination. There was marked distention of the abdomen. No pyloric tumor could be palpated. A rectal examination revealed no abnormalities. The child, having lost twenty-four ounces in weight, was examined under the fluoroscope. The stomach nearly filled the entire abdomen. Barium was introduced into the stomach by means of a catheter and examination fluoroscopically gave

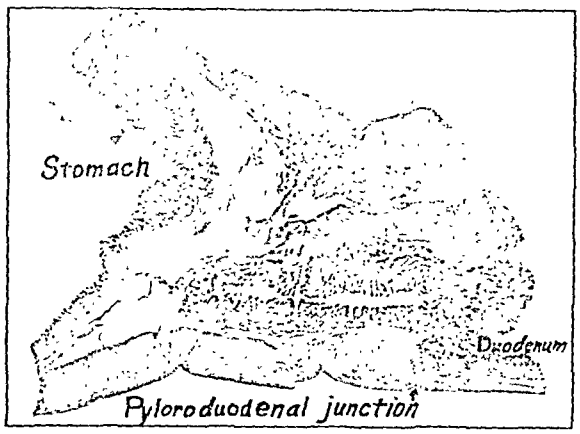


Fig. 1. Pyloroduodenal junction showing atresia of pylorus. Hematoxylin-eosin stain; x6.

further evidence of a markedly dilated stomach. Apparently no gas or barium passed into the duodenum. A barium enema revealed no abnormalities. A diagnosis was made of hypertrophic pyloric stenosis.

Treatment. The usual anti-spasmodic medical measures having been of no avail, it was deemed advisable to relieve the condition by surgical means. Using local ½% novocain, a 3 cm. upper right rectus incision was made through the abdominal wall. The stomach was four times normal size with a definite 1½ cm. tumor at the pylorus beyond which there was a marked reduction in the diameter of the small intestine. The large bowel was not entirely collapsed. It was thought best to do a Rammstedt type of pyloroplasty. A 1 cm. longitudinal incision was made over the central portion of the pyloric tumor the incision being carried through the serous and muscular layers until the mucosa bulged well. A small piece of gastrohepatic omentum was sutured to the inferior border of the pylorus so that the bulging mucous membrane was covered. The operation being finished, 30 c.c. of warm normal saline solution were poured into the abdominal cavity and the abdomen was closed without drainage.

Following operation, fluids given by mouth were not retained. The general condition at this time was critical and the baby expired thirty-six hours after operation.

Autopsy. There were no significant findings except those present in the gastro-intestinal tract. The esophagus was dilated to a diameter of 1 cm. Examination of the abdomen revealed an enormously dilated stomach with an enlarged and firm pylorus. Incision of the Rammstedt type of operation was present on the anterior aspect of the pylorus and was found to be satisfactory. A probe could not be passed from the pylorus to the stomach or vice versa. The small intestine was collapsed. The cecum was enlarged and contained some barium. The large bowel showed nothing of note.

Microscopic. Serial longitudinal sections studied microscopically revealed a 1 mm. lack of continuity in the lumen of the pylorus, 5½ mm. proximal to the pyloroduodenal junction. There was no evidence of epithelial-lined lumen joining proximal and distal pylorus.

DISCUSSION

For congenital atresia of the pylorus and the first portion of the duodenum, I would suggest that a long pliable wire within a catheter be passed down the esophagus into the stomach with the abdomen open. Once in the stomach, the pliable wire could be pushed a short distance beyond the catheter and placed against the offending septum. The proximal end of the wire would then be fitted into the usual handle of the electro-surgical unit, the power being turned on and off as desired. The catheter protected wire could be manipulated through the stomach wall by means of the right hand and the left hand could palpate the anomalous part to estimate when a suitable sized opening had been completed. In a very short operating time, an intra-intestinal method of producing gastro-intestinal continuity could thus be performed avoiding peritonitis which is so often fatal in the newborn.

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Submitted January 5, 1937.

ally as Editor of the American Journal of Digestive Diseases and Nutrition. His untimely passing leaves a void that will be difficult to fill.

Frank C. Yeomans, New York City.

It was with deepest regret that I learned of the death of Doctor Smithies. I know none of us can replace the tremendous energizing stimulus and intelligence he exerted over the activities of the medical profession, especially our gastro-enterological group and the Journal.

A. H. Aaron, Buffalo, N. Y.

I was shocked to learn of the untimely death of Doctor Smithies. I have known him for years as a courageous and indomitable fighter for those principles he regarded as right. Although never anxious for indiscriminate friendships, Frank Smithies had an unusual capacity for personal loyalty.

Curtice Rosser, Dallas, Texas.

Genial, brilliant and forceful Frank Smithies has been one of the outstanding figures in American gastro-enterology for the past two or three decades. He, perhaps, has done more to advance the scientific study of gastro-enterology than any of our confreres. His contributions to the literature on gastro-enterology have been valuable and stimulating to others of us engaged in the study and treatment of abdominal diseases. Perhaps the crowning piece of constructive work in Frank Smithies' career was his cooperation in the upbuilding of a high class journal devoted entirely to digestive diseases and nutrition. This publication will be continued and will receive the hearty support of every man interested in internal diseases.

Seale Harris, Birmingham, Alabama.

I was shocked to hear the news of the death of Doctor Smithies. He was one of the most dynamic and energetic men of my acquaintance. His passing is a loss of the first magnitude to the cause of scientific gastro-enterology in America. All of us who knew him marvelled at the amount of productive work he has been able to turn out, year after year. He was always a courageous leader, a sincere critic and an accomplished clinician. His editorial work on the American Journal of Digestive Diseases and Nutrition was his last major accomplishment and it will continue to be a monument to his memory and an evidence of his ability.

H. L. Bockus, Philadelphia, Pa.

I was closely associated with Doctor Smithies in gastro-enterologic work here in the Mayo Clinic a number of years ago. He always impressed me with his great native ability, industry, enthusiasm and studiousness. In addition to his scientific qualifications and achievements, his interests were wide. He was a model husband and a devoted father, and his genial personality endeared him to his friends. He was a prolific writer and his achievements in the field of science were enviable. These accomplishments, in addition to the fact that he was one of the founders of the American College of Physicians, and Editor of the American Journal of Digestive Diseases and Nutrition, which he also helped to found, should assure him a permanent place in American Medicine.

Geo. B. Eusterman, Rochester, Minn.

I was indeed shocked and grieved to hear of the death of Doctor Smithies. My contact with him dated back to 1917 when I was at the University of Illinois, College of Medicine. There, both as a student and a member of the faculty, I came in rather intimate contact with Dr. Smithies. In our class, at least, he was considered one of the finest teachers of medicine we had and we all looked forward to his classes and particularly to his clinics. He always treated his students as colleagues and I never saw him show anything but the kindest interest in their welfare. His lectures were beautifully organized and he made a profound impression on his students. To those of us who knew him personally his loss is great and we will remember him with affection.

T. B. Magath, Rochester, Minn.

The entire medical profession, and particularly those of us who have known him intimately and followed his work in recent years, grieves at the sudden and untimely death of Dr. Frank Smithies. He represents one of the figures making for real progress in medicine. His boundless energy and wealth of ideas stimulated many of his coworkers, professional friends and enemies, to continued improvement of methods used in professional practice and new fact finding. Frank Smithies had a personality which stimulated all who came in contact with it. He was instrumental in starting many medical advances which will live as monuments. Perhaps some of the most outstanding were his activity in the inaugurating of the American College of Physicians and his editorial activities for the American Journal of Digestive Diseases and Nutrition. We shall all suffer by his departure.

J. A. Bargen, Rochester, Minn.

I have been closely connected with the founding and subsequent development of the American College of Physicians as Regent, Governor and Secretary-General, and during a good part of that extended period I was in constant contact with Dr. Smithies. Those of us who had the good fortune to be in touch with College affairs at that time know full well that it was he, almost single handed, who saved it from disaster and set it upon the road to a highly successful and useful career.

Dr. Smithies for several years devoted more of his time, each day, to College affairs than to his private practice. More than this he spent for the College generously of his own money, at a time when the finances were in a precarious state. Of these personal expenditures he kept no account and for them he was never reimbursed.

Second only to his immediate family was the American College of Physicians, his chief concern in his daily life. The American College of Physicians owes Frank Smithies an everlasting debt of gratitude.

Wm. Gerry Morgan, Washington, D. C.

I have learned with profound sorrow of the death of Dr. Frank Smithies, an indefatigable worker, an outstanding clinician, a discriminating specialist, a voracious reader, a prolific writer, an efficient editor, a loyal friend, who will be sorely missed in the various fields of activities by the many with whom he came in contact. His death represents a severe loss to the profession which he adorned.

Irvin Abell, Louisville, Ky.

While I knew that Dr. Smithies had not been well for some time, I was terribly shocked to hear of his sudden passing away. Needless to say, I do not have to tell you what a tremendous loss our Association suffers and how grieved his very many friends both in the Association and at large will be on learning of his death. He was certainly a splendid fellow and always very frank. I had become very fond of him and admired him more and more for his tireless energy and enthusiasm under the load of the physical handicap that he bore so well.

Russell S. Boles, Philadelphia, Pa.

I was indeed shocked to learn of Dr. Smithies' death, because the last time I saw him he was so perfectly well, and it seems impossible that he is dead. The Journal of Digestive Diseases and Nutrition will undoubtedly suffer a great deal by his loss. I have known Dr. Smithies for the past twenty years, first learning to know him while I was an extern at the Augustana Hospital in Chicago. I have never known a man who deserves more credit to have accomplished the things he has in spite of his infirmity. He was strictly honest, thoroughly reliable, and a great friend of the young man. Even as a young extern

"In Memoriam"



FRANK SMITHIES, M. D., Sc. D., M. A. C. P., 1880—1937

Obituary

Dr. Frank Smithies passed away Tuesday morning, February 9, 1937, following a cerebral hemorrhage.

He was born in Elland, England, December 21, 1880, and came to the United States when a very young child and had his elementary school education in Philadelphia and Chicago. He was a graduate of the Calumet High School of Chicago and studied medicine at the University of Michigan from which school he was graduated in 1904. Following this he went abroad and studied at the University of Berlin and Guy's Hospital, London.

After returning to this country he taught at the Rush Medical College, 1904-05, and then at the University of Michigan, 1906-10. He then went to Mayo Clinic, Rochester, Minn., where he worked in the Department of Gastro-enterology from 1911-14. After this he returned to Chicago where he practiced Diagnostic Medicine with especial reference to Diseases of the Digestive System. From 1915-25 he was professor of medicine at the University of Illinois. He was Attending Physician, Henrotin Hospital since 1921; Chief of Clinic in Digestive Diseases, Municipal Tuberculosis Sanitarium, Chicago, 1927-30; Consulting Physician of the C. M. and St. P. R. R.

He made many contributions to the medical literature. His papers numbered well over one hundred, including his book on Cancer of the Stomach, published in 1916. He was Editor-in-chief of the American Journal of Digestive Diseases and Nutrition and Associate Editor of the American Journal of Syphilis (St. Louis), Annals of Internal Medicine (Lancaster), and American Journal of Tropical Medicine (Baltimore).

He was past president of the following societies: American College of Physicians, 1927-28; American Gastro-Enterological Association, 1929-30; American Society of Tropical Medicine, 1931-32; American Therapeutic Society, 1932-33.

His hobbies were reading and fishing. He collected many rare books and was particularly interested in books on arctic explorations, of which he had an unusually large collection.

In 1917 he was made a fellow of the American College of Physicians, and elected a member of the council of the College, and later created one of the four *Masters*.

Dr. Smithies did not seek honors, they came to him in recognition of his scientific attainments. He had been for many years a very active member of the American Gastro-Enterological Association bringing to its meetings many excellent papers always presenting clear cut, unequivocal statements which amplified and illuminated the subject. He was a past president of this association.

He understood so well people and motives, which, with his dynamic personality, aided him greatly in the practice of medicine and medical organization. His diligence and vision were a great influence in establishing the American College of Physicians on a permanent foundation.

Our Editor-in-chief, Frank Smithies, now belongs to the past, and as time goes on we will more truly know his distinctly journalistic qualities and his masterful knowledge of gastro-enterology. The latter was encyclopedic in scope and gave to our journal at once a preëmminence in its sphere.

Clement R. Jones, Pittsburgh, Pa.

In the death of Dr. Frank Smithies, the medical profession has suffered an unusual loss. As teacher and writer his ability was outstanding. His teaching of gastro-enterology was characterized by a vigorous and original approach to old problems, by clear, masterful thinking, and by lucid expression. These native qualities were made still more effective by a colorful personality. As a speaker before various national and state medical societies, his services were ever in demand, deeply appreciated, and cheerfully given. A keen, critical sense was one of his outstanding attainments; and he exerted a most stimulating influence upon younger medical men. As Co-Founder and Editor-in-chief of the American Journal of Digestive Diseases and Nutrition, he has made a lasting contribution. Truly, he was one of the outstanding medical figures of this generation.

John G. Mateer, Detroit, Michigan.

In the death of Frank Smithies the medical profession as a whole, and especially those devoted to intensive study of digestive problems, have lost a wise adviser and an acknowledged leader. His contributions have been many and varied in the field of diseases of the stomach and intestine, while his indomitable courage and indefatigable energy unquestionably have been of inestimable value to his many students, medical friends and patients. His loss is a very real one and will be deeply felt by everyone who has come in contact with him personally or who has been helped by his work and character.

Thomas R. Brown, Baltimore, Md.

The untimely demise of Frank Smithies robs science of a scholar of international stature, deprives mankind of a noted benefactor, and afflicts his friends with an irreparable loss.

It was a privilege to have studied under him at the University of Michigan, and a still greater privilege to have been an intimate friend for over thirty years. Friendship for Frank Smithies had a deep-seated foundation of admiration for his intellectual achievements. The list of his literary contributions to medical science, beginning in 1904, has been extensive. He was a leading authority on gastro-intestinal diseases, and his share in the alleviation of human misery shall never be accurately gauged. His tremendous intellectual activity, simultaneous with the exacting duties of a large practice, was the more astounding in that for many years he has been severely handicapped by infirmity and constant suffering. Even while ill, he was ever busy, carrying on many times on nothing but sheer courage. As a friend he was gold thrice refined. His loyalty, thoughtfulness, devotedness, tenderness were the flowerings of a fine spirit. A tribute of love and admiration to Frank Smithies is inadequate without mention of the lovely wife who for twenty-eight years helped and inspired him. To her and his lovely children we bring our sympathy and affection. May the esteem and love paid their husband and father by countless friends and patients help to solace their grief and soften the pain of his absence. Dr. Frank Smithies will live as long as friendship and gratitude blossom on this earth.

Thomas M. Joyce, Portland, Oregon.

In all my relations with him I was deeply impressed with his sincerity, his intellectual integrity and sound, well balanced judgement. Though chiefly concerned in the cultivation and development of his specialty—Gastro-enterology—he had a broad, panoramic view of medicine as attested by his early contributions and researches on goitre and in other fields. His enthusiasm and inexhaustible energy gave him a great capacity for productive laboratory and clinical research which found literary expression in the constant stream of publications that issued from his fertile pen, and in the numerous addresses and lectures which he delivered as a teacher and authority in his special field, much in demand all over the country. His bibliography will suffice to attest to his scholarship, to his

industry and to his devotion to the specialty which he so materially advanced and helped to elevate by his example and spirited leadership.

Rudolph Matas, New Orleans, La.

Medical science has met with a great loss in the passing away of Dr. Smithies and we who knew him personally are filled with sorrow.

Chevalier Jackson, Philadelphia, Pa.

The sudden death of Frank Smithies proved a tremendous shock to his French Colleagues, for we did not know of his illness, so unfailing had been his literary and scientific activities during the past months. Devotion of mind and heart to scientific advancement, industry, intellectual probity, executive power, yearning for scientific truth; his efforts to promote a better *entente cordiale* among physicians of all nations, and particularly between Americans and Frenchmen—these qualities and activities mark him out, in my opinion, as a truly great American physician.

As a student in 1921, and during subsequent clinical tours of England, France and Germany, Smithies' works on cancer, ulcer and nutrition are among the accepted things our masters quoted and desired us to translate. As secretary to Major-General Gouachon, and while on a tour of Hospital Investigation, I was thrown with Frank Smithies daily during a week or more in Chicago, and had the opportunity of gaining his ideas on medical interchanges with Europe. These ideas proved of value when I returned to France. His work as American representative of the "Association for Developing Medical Relations between American and French Physicians," has already borne excellent fruit. He saw the desirability of a closer relationship between the English and French medical institutions in Montreal. We in Quebec Province salute the Departed as a great man, who understood our problems and will always remember his brilliance, his sense of humor and his excellent judgment.

Jean LeSage, Montreal, Canada.

Frank Smithies possessed a dynamic personality; he could never be neutral; nor could he be indifferent; he carried his sovereignty beneath his own hat; his was a virile personality. It is interesting to note that his enthusiasms were always of a constructive trend; his ambition was to build; he spent his energy in constructive activities; he thrived in an atmosphere of flux, but always creative; he revealed in growth, whether orderly or riotous. Essentially an extrovert, yet he was of studious habit; an accomplished salesman, yet, withal of scientific bent; conscious of the power of propaganda, yet he worshipped in the Temple of Fact; a strange mixture of the pedantic and pragmatic. His most outstanding work, aside from making his mind a well-stocked granary, was the American College of Physicians. That organization is peculiarly the result of his labor; he kept it alive in spite of criticism and opposition that was, in essence, personal; he nursed it as a fledgling through the period of the World War; while it did not remarkably grow numerically under his guidance, it did acquire a hardihood that defied the ailments of childhood and permitted it to achieve maturity under the guidance of Stengel. As one who revolted under his leadership it affords an undisguised satisfaction to accord, thus, to Frank Smithies the credit for making an organization place for internal medicine. A brave heart, an unflinching spirit, an able leader and a great physician is gone. He had little peace in life; may he have it in abundance in death.

Virgil E. Simpson, Louisville, Ky.

It is with a sense of personal loss as well as of a distinct loss to Dr. Frank Smithies' many and varied interests in medicine that I learn of his death.

I came to know Dr. Smithies through several avenues. He was one of the profession's indefatigable workers, a man of great energy and ambition, an organizer of wide interests, a leader in progressive and aggressive medicine, a physician of forward vision and keen ability. His death will be felt beyond the immediate interests of our Journal. His energy will not be commonly found among us.

Kenneth M. Lynch, Charleston, S. C.

To me one of the most characteristic traits of Dr. Smithies was his intense, and still lovable, loyalty to those whom he looked upon as his friends. An absence of years made no difference with him. One picked up the thread of his relationship with Dr. Smithies where it had been interrupted as though it had never been severed at all, without any feeling on either's part of change incident to time and absence. Such a trait is born in a man; it can neither be developed nor submerged. And fortunate is he who possesses it, for it compels in return spontaneous loyalty on the part of others. In so intense, so pioneering a life, as Dr. Smithies lived, it doubtless smoothed out many trials and adversities that necessarily came to him. In his passing he has left his imprint on American Medicine to a degree a few only have equaled.

Noble Wiley Jones, Portland, Oregon.

The passing of Frank Smithies has left a gaping void in American medicine. The loss that scores of patients of his have sustained is small by comparison to that which we have sustained. He was the inspirational genius of "our Journal." It was only through his dynamic leadership that the unity of effort was achieved. His was the gift of inspiring the individual to greater efforts and of molding groups of soloists into an harmonious ensemble.

The Leader is gone but that indominatable spirit will always remain with us and we will fulfill our obligation to the great purposes of his life—and carry on.

Martin G. Vorhaus, New York, N. Y.

American Medicine has sustained a distinct loss in the passing of Frank Smithies. An enthusiastic, unbiased investigator, a thorough, kindly teacher, a clinician of the first rank, his publications were known and quoted througout the world of medicine, his methods of diagnosis and treatment were recommended in leading text-books. As co-founder and Editor-in-chief of the American Journal of Digestive Diseases and Nutrition he made a monument for himself which, with the impetus given by his three years of indefatigable labor, should remain a permanent memorial. Organized medicine long since recognized the worth of this remarkable man and heaped upon him, in his all-too-brief career, honors which but few great men have attained in a much longer lifetime. He enjoyed a full life, worshiped by his family, loved by his many friends, and his passing leaves a void which will be difficult to fill.

A. R. Andresen, Brooklyn, N. Y.

The name of Dr. Frank Smithies was known wherever scientific medicine was practiced. Dr. Smithies, throughout his lifetime, was a devout and indefatigable worker for medical progress. His deep interest in the gastrointestinal phase of medicine has been responsible directly or indirectly for many advancements in this field of work. A measuring stick of the scope of Dr. Smithies' interests, his versatility, and his achievements may be seen in his work as Editor-in-chief of the American Journal of Digestive Diseases and Nutrition. A personal friend, a friend of medicine, and an outstanding figure in the medical profession has been removed by the death of Dr. Smithies.

Francis D. Murphy, Milwaukee, Wis.

Dr. Frank Smithies always impressed me as an outstanding forceful personality in the medical world. His numerous and valuable contributions to the literature were lucid and logical and were supported by a wealth of clinical experience. He demonstrated his genius as a leader and organizer in several medical associations and especi-

Life passes, we go, others come and fill the ranks. The filling of the ranks, however, is not a mere automatic, mechanical procedure. There are foot-prints left behind which are often inerasable and which point the way to the newcomers. It is these footprints which lead to a certain goal; this is all that we can leave behind, footprints pointing the way. In the case of Dr. Smithies, our beloved friend, there were left clear footprints indeed. His inexhaustible energy, his jovial nature, his inspiration to others are the things which will always stand out in the minds of those of us who had the privilege to know him. May his foot-steps ever stand out and remind us to follow the way which he all through his energetic life has pointed out.

Henry J. John, Cleveland, Ohio.

The shock occasioned by Dr. Smithies sudden passing is too great for us to properly evaluate his contribution to medicine.

As a young man, he said, "You fellows can play golf and have other hobbies, but mine is writing."

His mind was essentially creative in character. He sat at his desk and planned the organization of the American College of Physicians and carried it through almost single handed. Our Journal is in no small part a creation of his genius, and we link its success with his untiring energy and enthusiasm. It is a fitting monument to his memory.

Horace W. Soper, St. Louis, Mo.

In the death of Frank Smithies, Gastro-enterology has lost one of its valuable and enthusiastic disciples. He was a clinician who thoroughly understood the fundamental science of his art. His letters and words of encouragement have stimulated numerous young investigators in the science of digestion. He worked unceasingly for the advancement of his specialty in our country. He supported and originated many worthwhile efforts to promulgate the better fortunes of his chosen field, with the advancement of which his name is inextricably interwoven. To him the laurels of accomplishment are due and those who know his good works mourn his passing.

A. C. Ivy, Chicago, Ill.

I knew our late lamented Dr. Frank Smithies for many years, and held him in affectionate regard.

His alert mind and keen intellect were always felt and appreciated. He had an outstanding capacity for work and statistical classification. His writings were trenchant, and full of snap and vigor.

As a man, he displayed a charming personality and a most entertaining contact. As a physician, he showed deep knowledge of human nature and of disease. His mind covered with celerity the many angles of clinical studies of the sick. He showed wisdom and resourcefulness in diagnosis and therapy. As a companion, he was witty, affable, and humorous. As a friend, he was affectionate, helpful and unselfish.

He will be greatly missed by members of the medical profession, and his memory will have a lasting place among them.

Allen A. Jones, Buffalo, N. Y.

It has been my privilege to have known Frank Smithies for a quarter of a century, at first merely as a colleague and subsequently as a greatly esteemed friend. I find myself—like many others—mourning his death in a very personal sense. Smithies possessed a strong personality, a determined will and a tireless energy that was all the more remarkable because of physical handicaps. As is common to many strong characters Smithies made some enemies and his convictions sired many critics. I have come to realize, as the years have passed, that most of his critics were over-captious and some of his enemies were far lesser men—even as I—if they ultimately failed to find the amazing good in the man they one time disliked.

As a well rounded clinician and particularly in regard to his special interest in gastro-enterology, as a sub-division of internal medicine, Dr. Smithies climbed well up the ladder and would have gone even further had his Kismet allowed him larger opportunities to develop his natural skill in clinical research.

I keenly recall my first impression of the man some twenty-five years ago when he rose as a floor discussor of a symposium on some gastro-intestinal topic at a meeting of The American Medical Association. The principal speakers were then men of national reputation and Smithies was relatively unknown. Always an able speaker on his feet, and on this occasion reinforced by data of several hundred cases of the topic under discussion, his remarks were direct and to the point and created disquietude on the part of the symposium principals in their efforts to suitable reply. On returning to his chair—next to mine—he handed me the ledger containing the data set down in his meticulously careful way—the data running into several hundred thousand items which he had abstracted and condensed to a ten minute time limit. This was my first impression of Frank Smithies and it gave a significant insight into the painstaking detail-collecting metier that was characteristic of him.

He was literally an indefatigable worker and I believe an honest searcher after the medical truth. I imagine that this may explain his penchant as a "debunker." Smithies had faults—who has not—that created misunderstanding and made his critics race to counter attack. In some respects he was intolerant of the views of others but tempered by a proper and wholesome intolerance of sloppily done investigative work by which the investigator arrived at premature or unsound conclusions.

Dr. Smithies' personal contributions to medicine, and to gastro-intestinal medicine in particular were too numerous to mention—most of them were timely as regards topics of the period, some could be appraised as ahead of his day and a few were so brilliant in their conception that they may prove to be contributions of lasting value to medicine. Among the most interesting were his views regarding the etiology and the life history of peptic ulcer, a subject which was always one of his "pets."

As an organizer and executive leader he was most able. The record of his career as set out in the editorial by Dr. Clement R. Jones amply attests this ability. His leadership—together with others—in rescuing the American College of Physicians when it was sinking into merited oblivion and helping to build it up to its greatly improved present position and a secure future, will remain as a monument to his having lived. Likewise, his efforts regarding the welfare and progress of the American Gastro-Enterological Association and particularly his Editorship of the American Journal of Digestive Diseases and Nutrition, under handicaps physically and economically that would have appalled a less courageous man, can be counted as real achievements.

He was the kind of man who could look adversity in the face and keep on smiling and it can truly be said that he died with his boots on. Such men are not easily missed or their places readily filled.

B. B. Vincent Lyon, Philadelphia, Pa.

In the passing of Dr. Frank Smithies the profession has lost an unusually able clinician and the community is deprived of a man of many parts, a skilled administrator and organizer, and this Journal has lost the distinctive genius of a devoted Editor-in-Chief.

Dr. Smithies will be missed by very many friends for he had a genius of attracting to himself loyal and devoted adherants to whatever cause he was interested in.

C. T. Martin, Montreal, Can.

Doctor Frank Smithies was one of the pioneers in this country in developing an interest in tropical medicine and human parasitology. At a time when few practitioners of medicine were familiar with parasitic diseases, Doctor

I felt that I could always approach Dr. Smithies at any time for his counsel. His ability to study carefully and evaluate a particular case was surpassed by none, and in the treatment of a case he was always careful to see that the younger men with him got to examine a patient and profit by his experience.

Alton Ochsner, New Orleans, La.

It was with great surprise and sorrow that I noted the passing of Dr. Frank Smithies on February 9, 1937. I have been personally acquainted with Dr. Smithies for many years and always regarded him as one of my best friends. During this time, Dr. Smithies has been one of the foremost clinicians in the United States and contributed much to our knowledge of clinical medicine. It is with a sense of distinct personal loss that I am writing this, for, through all the years, our association was most pleasant. Aside from his professional standing and ability, Dr. Smithies' kind heart endeared him to all of his associates and friends.

Charles F. Craig, New Orleans, La.

Frank Smithies stood for energy, enterprise and hard work. At the meetings of the American Gastro-Enterological Association we looked to him for keen and critical discussion of any paper, and, at times, with his "satirical diatribes," as Dr. Pilcher called them, and his profound knowledge of the subject, he tread heavily on the toes of some of the contributors. But he wanted the truth brought out and his criticisms were not personal. In the reorganization of this Association he was an important instrument. During my presidency he was secretary, and though confined to the hospital with a long siege of illness, carried on the needed activities and arranged a program of a quality that up to that time had not been approached. His artistic sense showed in his hobby for old ship models. As Editor of the Journal he consulted all of us on the Editorial Board, and repeatedly sought advice and suggestions from one or the other.

Walter A. Bastedo, New York City.

The passing of Doctor Frank Smithies is a tremendous loss to American medicine. The public has lost one of the leading physicians in this country, and the profession has lost a dynamic personality, a powerful leader and a great teacher.

E. Perry McCullagh, Cleveland, Ohio.

It is with a feeling of personal loss that I learn of the death of Dr. Frank Smithies. An acquaintance which began thirty years ago when Dr. Smithies and I were both living in Ann Arbor has become more intimate within the last few years, since the organization of the American Journal of Digestive Diseases and Nutrition, and has enabled me to see and admire the surprising energy which Dr. Smithies has put into all of his medical work. That others have been impressed by his ability and by this same driving energy is amply demonstrated in the honors which have come to him which have included the Presidency of the American Therapeutic Society, of The American Society of Tropical Medicine, of The American College of Physicians, The American Gastro-enterological Association, assignments of honor as well as responsibility on the Scientific Assembly of the American Medical Association, and the Ribbon of the Legion of Honor of France. Gastroenterology, and medicine as a whole, have lost a man of achievement.

Warren T. Vaughan, Richmond, Virginia.

America has indeed lost one of its distinguished physicians and experimental medicine one of its most enthusiastic advocates. Dr. Smithies had many admirable qualities but in my estimation one of the most outstanding was his unfailing interest in and courtesy toward young men who showed promise of research ability. He was always interested in people who did things and as his whole life was one of accomplishment he indeed served as an inspiration to those who are trying to do worth while things.

Edward J. Van Liere, Morgantown, W. Va.

Ever since my association with the American Journal of Digestive Diseases and Nutrition, I have been impressed by Dr. Smithies' high sense of duty to his position as Editor. He was most energetic in fulfilling his duties as Editor-in-chief and in my correspondence with him, his frankness and earnestness made a great impression.

Howard F. Root, Boston, Mass.

It was with the utmost sorrow that I learned of the sudden death of Frank Smithies. From the time of my first acquaintance with him at the University of Michigan, his life, struggles and accomplishments have always been an incentive to more appreciation and effort on my part. We shall miss his judgment at our councils, his constructive criticisms, his cordiality and his virile will to progress. I wish there could be more like him to whom we might look for advice and stimulation in this chaotic world in which we live.

James T. Pilcher, Brooklyn, N. Y.

In the death of Doctor Frank Smithies, American medicine has lost one of its outstanding personalities. Physically handicapped but mentally alert, Doctor Smithies was a great organizer, a thoroughly trained internist, an excellent writer and a true friend. I am sure that I voice the sentiments of all those interested in the advancement of knowledge pertaining to the gastro-intestinal tract when I say that we have lost a champion who will not be easily replaced.

Porter P. Vinson, Richmond, Va.

The standing and ability of Dr. Frank Smithies in the medical profession are widely known and appreciated and his death constitutes an almost irreparable loss not only to the clientele whom he served but also to those who have long profited by his written communications on medical topics. No others, however, will feel his loss so keenly as his host of friends who knew and loved his personality. Something is gone out of their lives that will not soon be replaced.

William Fitch Cheney, San Francisco.

Frank Smithies has been one of the leading men in digestive diseases for more than a generation. He was a tireless worker, a great organizer, and ever since his early days at the Mayo Clinic has stimulated and carried on an immense amount of valuable clinical research. His genial personality, native talent, and immense experience won him a host of friends all over the country and made him a leading consultant in his special field. This Journal owes its steady progress and leading position largely to his devotion and tireless efforts as Editor-in-chief. His heroic attitude in the face of long disability and finally of serious illness has been an inspiration to us all. He will long be remembered not only for his scientific skill and vast clinical experience, but for his great courage and kindness of heart.

Franklin W. White, Boston, Mass.

Many years ago when I became a member of the American Gastro-Enterological Association, I had the good fortune to meet Dr. Frank Smithies. He impressed me as a man of high, intellectual attainments, deeply interested in his work. While fearlessly critical he was always fair and just. Once you had obtained his support, he was unfailing in his interest and loyalty. We all know how devoted he was to his work with the American Journal of Digestive Diseases and Nutrition.

He will be sadly missed; and will always remain in our memory as a distinguished figure among his colleagues.

Jerome M. Lynch, New York, N. Y.

reff upon the basis that the small intestine could not tolerate and would not accept an acid stronger than from 0.1 to 0.15% HCl. While, undoubtedly, regurgitation of duodenal contents plays probably the most important role in the neutralization mechanism, one cannot escape proper evaluation of the work of Shay, Katz and Schloss (10) who have shown that regurgitation from the duodenum is even greater when alkalis (1-1½% $NaHCO_3$) are introduced into the stomach than when either weak or strong acids are used. We have frequently noticed that the greatest amount of regurgitation occurs in patients with achylia gastrica during a plain water meal. Furthermore, we have been unable to change the color of bromsulphthalein with the regurgitated duodenal contents, even in the presence of achylia gastrica, although this dye changes color at a pH of 7.2. Therefore, it is doubtful if the duodenal content is sufficiently alkaline to *markedly lower gastric acidity even in the presence of* considerable regurgitation. Reference to Figure 2, Graph II, reveals an increased neutralizing power in the presence of marked pyloric obstruction in both cases where duodenal regurgitation is inhibited. McCann (*Am. Jour. Physiol.*, 89:483, 1929) utilizing the Mann-Williamson operation which shunts all duodenal contents into the terminal ileum and short circuits the gastric contents into the upper jejunum, found that the neutralizing power of the stomach remained the same before and after operation. Since Hill and coworkers (*Am. Jour. Physiol.*, 106:381, 1933), using isolated pyloric pouches, have shown that the secreted mucus is neither sufficient in amount or alkalinity to account for the acid reduction, we must give considerable attention to the possibility of resorption or diffusion of hydrogen ions through the stomach itself or that the stomach is actually capable of secreting an alkaline juice as advocated by Author.

That dilution plays some part in the mechanism is indicated by adding a coloring matter (sodium salt of phenolsulphonphthalein) to the acid test meal and determining its concentration in the fractional specimens by means of a colorimeter. The strength of the acid in the meal and fractional samples was determined by chemical analysis and not by titration. It was found that from 55 to 60 per cent of the reduction was due to dilution and 45 to 50 per cent due to neutralization. Both clinical and experimental recent reports tend to show that the emptying time of the stomach plays very little if any role.

The work of Elman and McLeod and of Levy in connection with ulcer and pylorospasm has been confirmed. Since the neutralizing power in the other diseases studied was within normal variations with the exception of liver and gall bladder disease, it would appear that its diagnostic value in ulcer is even greater and more specific than has been previously emphasized.

A modified technique has been introduced which is less difficult of application by the individual clinician who must refer his cases to a laboratory for analysis since by this technique both the secretory and neutralizing curves can be determined at a single sitting. Total volumes of the test solutions have been reduced which has eliminated discomfort and frequent vomiting both of which are aggravating factors to accuracy of the tests.

CONCLUSIONS

1. The clinical value of the neutralizing functional test of the stomach in ulcer and pyloric spasm as established by other investigators has been confirmed. It apparently is of little or no value in other gastrointestinal and several general diseases investigated in this study except the possibility of liver and gall bladder pathology.

2. By modifying the technique of Elman and Levy both the neutralizing and secretory tests can be accurately performed at one appearance of the patient.

3. Evidence is submitted suggesting that the regurgitation of duodenal juices, while undoubtedly the main factor, is not the only one in the mechanism of neutralization.

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The Acidity Reduction Test Versus the Fractional Test Meal*

By

FRANK L. APPERLY, M.A., M.D., D.Sc.

RICHMOND, VIRGINIA

THERE is now abundant evidence that the rate at which acid in the stomach is diluted and neutralized is a much clearer indication of gastric function in health and in dyspepsia than is the degree of acidity alone. The reasons for this will be discussed later.

In 1914 Boldyreff (8) first showed that when acid is placed in a dog's stomach the acidity is rapidly reduced. (Fig. 1). This fact was not, so far as I am aware, applied to the investigation of the human stomach until 1923, when I showed that there was a

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Submitted November 12, 1936.

Smithies called attention to their importance and applied modern methods of diagnosis and treatment in his practice. For many years he took an active interest in the American Society of Tropical Medicine and was elected president in 1931. He also contributed generously to the support of the Society by special donations. As the finest type of gentleman and as a genial, big-hearted friend Doctor Smithies will always have an honored place in the memory of his colleagues.

Henry E. Meleney, Nashville, Tenn.

The death of Dr. Frank Smithies has removed from American gastro-enterology one of the most inspired and inspiring figures. The presence of Doctor Smithies at a medical meeting was always an insurance that there would be a complete discussion of all correlated work, Doctor Smithies' knowledge of medical literature being most extensive, and also that no unsound doctrine would escape keen and complete analysis.

He was wont to say that his physical handicap gave him greater opportunity and desire to study, and this fact redounded to the advantage of all who had professional and social contact with him.

The American Journal of Digestive Diseases and Nutrition, his long cherished dream, is now a most fitting memorial to him, and no greater future for the Journal can be desired than that the spirit of Doctor Smithies live on for many years in its pages.

Sara M. Jordan, Boston, Mass.

The great loss sustained in the sudden passing of Dr. Frank Smithies will be sorely felt both by clinicians, particularly the gastro-enterologists, and by experimental investigators. Dr. Smithies' outlook on medicine was broad; he fully realized the important part which the fundamental sciences play in the progress of medicine and he kept in permanent touch with them, as witness the so-called "Smithies gastric ulcer diet," based on physiological principles. He himself called this the "physiological rest method" (cf. *Amer. Jour. Med. Sci.*, 153, p. 547, 1917) and denounced the method of alkali therapy long before any experimental evidence was obtained that alkali stimulates gastric secretion. That Dr. Smithies was a "physiologically minded" clinician was clear from the general editorial policy pursued by him as Editor-in-chief of the *American Journal of Digestive Diseases and Nutrition*. His aim was to combine within one journal all that was theoretically or practically important in the field of gastro-enterology. Once when submitting to him a purely physiological article, I expressed the doubt that perhaps such an article would be unsuitable for a medical publication. He replied as follows (on 3rd Dec., 1934): "I, personally, and everybody with whom I have talked, appreciate your sending original articles to this publication. I know that a lot of them could have been printed in other journals but then the practitioner probably would not have read them. As a sort of slogan for our publication we have adopted in our propaganda announcements the phrase 'The Magazine Where Investigators And Practitioners Meet.' This slogan expresses exactly what I had in mind when this Journal was started. . ."

Therefore by the death of Dr. Smithies not only is the medical profession deprived of one of its most prominent members, but the theoretical sciences have lost a friend who appreciated their importance and recognized their true value in relation to practical medicine.

B. P. Babkin, Montreal, Canada.

I met Dr. Frank Smithies for the first time at the Mayo Clinic when attending the meeting of the American College of Physicians, in 1922. I took a great liking to this perfect gentleman who was then Secretary-General to the College, and I admired very much his courtesy.

I wrote him on several occasions, since 1931 particularly, after a trip to Paris, with the purpose of organizing annual English clinical courses in the French Hospitals, which were to be given under the auspices of l' "Association pour le Développement des Relations Médicales entre la France et les Pays Amis" (A.D.R.M.) founded by Professor Henry Hartmann, and president ever since by this well-known Parisian surgeon.

On my return to Montreal I thought that Dr. Smithies was one of the many American physicians who could tell me whether such a similar organization would meet general approval in the United States. Dr. Smithies' answer contained such appropriate advices on the matter that I sent copies of his letter to Professors H. Hartmann, E. Sergent, G. Roussy and some other of my friends members of l'A.D.R.M. in Paris. All eminent medical authorities of Paris and France got acquainted since with Dr. Frank Smithies whom they admired for his "Franc parler" and generous contribution towards the English clinical lectures in Paris. I personally know that Dr. Smithies has been constantly in correspondence with his French confrères up to his death.

I had, about that time, founded in Montreal the Canadian section of l'A.D.R.M. with the cooperation of Dean A. Primrose of Toronto University, C. F. Martin, Dean of McGill University, Louis de Lotbiniére-Harwood, Dean of l'Université de Montréal, A Rousseau, Dean of Laval University, Quebec, and many other colleagues. The following year Dr. Smithies organized the American section of l'A.D.R.M. with the collaboration of Drs. James R. Arneill, Lewellys F. Barker, Harlow Brooks, George Crile, Maj. Gen. Hugh Cumming, A. U. Desjardins, George Dock, Reginald Fitz, Maj. Gen. M. W. Ireland, N. W. Jones, W. McKim Marriott, Martin E. Rehfuss, William J. Mayo, J. H. Musser, Carl V. Weller and others.

It was through the requests of Professors H. Hartmann, E. Sergent G. Roussy, E. Rist and other members of l'A.D.R.M. in Paris, jointly with the French Council in Chicago, that *la République Francaise* bestowed on Dr. Smithies the decoration of Chevalier de la Légion d'Honneur. I personally know that he heartly appreciated this delicate attention of his Parisian friends and that he was proud of the little red ribbon he constantly wore.

I must say that it was in 1933 that I had the second opportunity to meet Dr. Frank Smithies when he came to Montreal to attend the first Canadian session of the American College of Physicians. I hope every Fellow of the College who was present still believes it was a particularly interesting meeting, because they had the opportunity to see in our City two medical schools: one of McGill University and the other of l'Université de Montréal, having both their personality and traditions. McGill has always been known as a prototype of the English Universities, while l'Université de Montréal takes its own inspiration in its French ascendants, the Universities of France. Montreal is a living example of the "good entente" existing between its citizens of French and English origins. Dr. Smithies and his colleagues were then interested in both medical schools and their respective teaching hospitals where they attended clinics during this memorable meeting of the College.

Dr. Smithies and many other Fellows were welcomed in the Hotel-Dieu, Notre Dame, Ste-Justine and other French speaking hospitals where they delivered special clinics. I remember how pleased Dr. Smithies was after meeting Prof. Pierre Masson, previously of Strasbourg University, France, in his laboratory where he had with him a long talk on the pathology of cancer of the stomach. Prof. Pierre Masson was also very much interested with Dr. Smithies' remarks on pathology.

It was through Dr. Smithies together with Dean C. F. Martin and Prof. J. C. Meakins of McGill, that the College invited Prof. E. Rist, the well known specialist on tuberculosis, of Paris, to attend this Canadian meeting of the College. I am sure all the members of the American College of Physicians who were then in Montreal

remember the great success of Prof. Rist in his clinical lectures at Notre-Dame Hospital and at the general meetings at the Windsor Hotel, specially on account of his clinical science and his perfect knowledge of the English language.

It was my privilege on the same occasion, as President of the Canadian section of l'A.D.R.M. to entertain at a luncheon, at Le Cercle Universitaire, in honor of Dr. Frank Smithies, President of the American section of l'A.D.R.M., and Prof. E. Rist, member and delegate of l'A.D.R.M. in Paris. Some of the most prominent members of the American College of Physicians and representatives of McGill and l'Université de Montréal, as well as the French Consul in Montreal, and two Hon. Ministers of the Quebec Government were present.

The medical profession of the United States has suffered a great loss by the premature death of one of its most representative members. Dr. Smithies' numerous admirers in Paris have, I am sure, learned with deep sorrow of the sudden departure of their grand American friend and colleague.

Dr. Smithies' close friends and collaborators will appreciate his numerous contributions to medicine and his everlasting enthusiasm in the organization of the American College of Physicians and his work on the "American Journal of Digestive Diseases and Nutrition" in which he was so kind to associate some of his French Canadian friends of Montreal.

I am very proud to have been called upon to say a few words on this remarkable physician who will remain as a living example of an indefatigable worker, an honest man and a most devoted friend. It is on the tomb stone of such men that one may engrave: "HIC JACET VIR PROBUS."

J. E. Dubé, Chevalier de la Légion d'Honneur,
Montreal, Canada.

After I came into this country two and one-half years ago, I met Doctor Smithies on several occasions, none of these meetings lasting less than two hours, and I always left the room with a strange feeling of surprise and admiration. I felt his appreciation of "humanistic education" (I think this is an adequate translation of the German "Humanistische Bildung"), which evidently he had had in largest extent. I felt his ability to follow and to appreciate new ideas. I have considered him as one of the most perfect gentlemen I ever met. I always left him not only encouraged, but enthusiastic, full of confidence in the future of my own ideas, because he seemed to share them. That he was able to show me this confidence, proves that he not only was a gentleman but that he also was full of that natural friendliness which makes the great physician, which is inborn and can never be acquired. How will it be possible to replace him as Editor-in-chief of the American Journal of Digestive Diseases and Nutrition which was raised in two years to the leading periodical of its kind in the international scientific world? His successor will have a hard task; but we, his collaborators, should promise whoever he may be, to support him by all means to honor the memory and the work of unforgettable Dr. Frank Smithies.

Rudolf Schindler, Chicago, Illinois.

My intimate acquaintance with the late Frank Smithies began in the summer of 1933, when I called at his office for an informal chat and discussion of matters gastroenterological. I had known him professionally for a number of years and we had a few medical cases in common. I had always been impressed with the thoroughness of his clinical work. He had a flare for sizing up the psychological as well as the physical status of his patient. His patients were bound to him always by so strong a bond of confidence, that it was nearly impossible for another physician to fill his place even temporarily. He exacted and obtained from most of his patients a degree of regimentation, where it was necessary, such as I had never before seen or believed possible. He devoted a good deal of time to what at first often seemed insignificant phases of the illness. He had a distinct clinical instinct for diagnosis and used X-ray and other laboratory aids as mere secondary guides. His letters to physicians reporting on referred cases were exhaustive, and his instructions to patients were extremely detailed.

I called on him in August, 1933, to ask his opinion as to the advisability of starting a Journal in gastro-enterology and explained to him that this idea had been in my mind for a number of years. He gave me a quizzical, penetrating glance and asked, "why in h—— should you want to do that?" I confessed that my motives were as strong as they may have appeared ill-timed. The depression was then obtrusively present. I assured him, however, that I could interest publishers, and this fact obviously surprised him. Immediately, he decided to take the matter seriously, and it was not more than two weeks before he had assembled the Editorial Council, while I in the mean time made financial and printing arrangements.

During the four years that have passed, we worked in close harmony. Dr. Smithies was self-sacrificing in his work. Last summer, while ill and unable to work, he maintained touch with my office at all times. He even assumed the work of a technical editor, believing that his own personal touch was essential to the undertaking.

It is unanimously admitted today that Frank Smithies, as Editor-in-chief of this Journal, did an excellent piece of pioneering work. He did it thoroughly, with the vigor for which he is famous and he did it cheerfully and consistently. If he had strong dislikes, he also possessed very unusual fidelity to his accepted friends. In his contacts, it may be said, that he left no one cold; for his personality was an unusual blending of prejudice and loyalty. Above all, he was one of those rare men, whose unquenchable enthusiasm burned like a light, emphasizing its brilliance by its own untimely extinction.

Beaumont S. Cornell, Fort Wayne, Ind.

ANNOUNCEMENT

Soon after the death of Dr. Frank Smithies, Editor-in-Chief of this Journal, a slightly different plan of editorial management was decided upon. Following the practice of a number of leading medical journals in America, the position of Editor-in-Chief was abolished and responsibility placed upon a group of men comprising an Editorial Board. The members so far appointed are: Walter C. Alvarez, Rochester, Minnesota; Burrill B. Crohn, New York, N. Y.; Henry L. Bockus, Philadelphia, Pa., and Sara M. Jordan, Boston, Mass. The position of Supervising Editor is still retained by the writer. All manuscripts submitted for publication should be mailed to Dr. Cornell at 116 East Berry Street, Fort Wayne, Indiana. They will be sent at once for review, suggestion, criticism, and acceptance or rejection to appropriate members of the Board and Council. A technical editor will be appointed for such revision of articles as is considered necessary. It is felt that this method of editorial management is appropriate for this particular journal. To readers we may give assurance of a steady inflow of excellent contributions from many sources. To authors, we may state that we are still in the desirable position of offering quick publication. Furthermore, it is felt that suitable and adequate adjustment

has been made; and that the Journal, ably piloted by Frank Smithies through its early years, will continue to progress under the expert guidance of the Board and Council.

Beaumont S. Cornell, Fort Wayne, Ind.

Early in February, Dr. Henry J. John of Cleveland, Ohio, was given the Charles Eisenman Award of the Jewish Welfare Federation for his work in creating and maintaining Camp Ho-Mita-Koda for diabetic children. This work of Dr. John's for youthful diabetics has deservedly received wide recognition for a number of years. He has diverted the $750, which accompanies the award, to the work of the Camp.

NOTICE

The Annual Meeting of the American Gastro-Enterological Association will be held at the Hotel Claridge, Atlantic City, N. J., on Monday and Tuesday, June 7th and 8th, 1937. Please make hotel reservations at once.

Book Reviews

Physiological Chemistry. By J. F. McClendon and C. J. V. Pettibone, sixth edition, C. V. Mosby Co., St. Louis, 1936. 451 pages, 34 illustrations.

THE first section of this text, amounting to 322 pages, is devoted to exposition of the subject matter of physiological chemistry; the remainder (Section II) contains instructions for laboratory exercises. This is the first revision since 1931, the book having been issued originally in 1917. Except for certain subjects, the exposition is elementary and in many respects incomplete. Although the liver is the center of many types of intermediary metabolism with which physiological chemistry is concerned and which is important for the medical student and physician to know, the word "liver" is not mentioned in the index.

In these days of rapidly expanding knowledge in the fields of physiology and biochemistry, the problem of selection of subject matter to be presented to medical students in these subjects is a serious one. In the case of this book it is believed that the authors err in presenting too little of the subject matter of biochemistry, in view of the fact that most students now admitted to medical schools have had courses in organic chemistry and quantitative analysis. They must know considerable biochemistry in order to understand the metabolic disturbances that occur in so many diseases, and to interpret and understand the biochemical methods used to detect functional disturbances.

The book has the merit of simplicity and lucidity. It will serve as a good introduction to the subject of biochemistry, or as a basis upon which to build a more complete and essential knowledge of the subject. It is of little value as a reference source.

A. C. Ivy, Chicago.

Knud Faber: Gastritis and Its Consequences. Oxford University Press, London, etc., 1935. 119 pages, 48 illustrations.

THIS monograph, by Knud Faber, Professor of Internal Medicine in the University of Copenhagen, on gastritis most likely will become one of the classics of gastro-enterology. The author writes: "It is possible that the exposition I have given in these lectures may be considered to have too much of the stamp of my own personal views, which are not shared by all." This certainly is true, and exactly this quality of the small book increases its value immensely. Every page challenges the expert reader, every sentence could be discussed, nothing can be found of the smoothness of a usual textbook containing only ascertained facts. A tremendous experience becomes visible in every line, in fact, the experience of a whole human life. It must not be forgotten that since 1898 Knud Faber has been almost the only clinician to emphasize the existence, frequency and importance of gastritis. Very few workers sustained his opinion, and for 25 years he stood alone continuing his work and his fight. Only with the advent of routine gastroscopy in 1923 and with the work of German pathologists did the situation change. It changed so completely that now gastritis is considered the most frequent gastric disease. Knud Faber's final triumph is a complete one, but his book almost does not mention these events; the modesty of the aged author is remarkable.

The book is composed of three parts corresponding with three lectures delivered at Guy's Hospital Medical School in November, 1934.

In the first part: *"Acute and Chronic Gastritis"* Faber emphasizes the frequency of stomach diseases. Among 120,000 members of the health insurance societies of Denmark, 10%-13% had gastro-intestinal diseases, while only 1.3% had cardiac diseases. Because most of the gastric diseases are not fatal they persist longer and may accompany a patient through a long life. After short historical considerations, Faber describes his famous formalin injection method for preserving the stomach after death. Immediately after death, 500 c.c.m. of formalin solution were injected into the abdomen, and an excellent fixation of the tissue was obtained. Nevertheless, the interpretation of the pictures of the gastric mucosa found microscopically was not easy because dilatation of the stomach and post mortem changes often gave the impression of more advanced atrophy than really existed. Faber then describes the method of Konjetzny, Kalima, Puhl, who examined microscopically freshly resected specimens, but who naturally could examine only the antral part of the stomach. The sudden evolution of gastroscopy in Germany is described and it is stated that those investigators (Schindler, Gutzeit, Henning) claimed that chronic gastritis has been shown to be extremely common.

On one page the description of the normal histology of the stomach is given, chiefly derived from examinations in newborn children. This picture almost never is found in adults, yet Faber seems to be inclined to

call all differences from those in the stomach of the newborn, "gastritis."

An excellent description of acute gastritis is given. Beaumont's famous report on the Canadian St. Martin is quoted extensively. Faber differentiates between "irritation gastritis" and "hematogenous gastritis." The *irritation gastritis*, a very common disease, can apparently be completely cured, but generally leaves behind traces of inflammation. Renewed acute outbreaks finally lead to chronic gastritis. Faber has an extended experience on the *"hematogenous,"* acute gastritis. Numerous observations made in cases of typhoid fever, diphtheria, influenza, pneumonia, etc., illustrated by photographs, are convincing. A thorough description of the microscopic changes is given, but acute *"irritation"* gastritis does not lend itself readily to anatomical investigation, since it is not a fatal disease. In chronic gastritis a combination of acute and chronic processes will be found. Two distinct forms are encountered, namely, "chronic erosive gastritis" and "diffuse pangastritis which tends toward atrophy." It is important that Faber states that chronic erosive gastritis is best known from examination of resected parts of stomachs operated on because a chronic ulcer has been diagnosed, and that diffuse atrophic gastritis is best studied in post mortem specimens. The results obtained with the formalin method in the second form are convincing. The erosive gastritis usually is pyloric gastritis. The microscopic picture is of an acute character, the erosions usually not penetrating through the mucous membrane. However, also chronic changes are found. The mucosa in chronic diffuse *pangastritis is smoothed out, the color is pale, no* erosions are seen, microscopically there is no acute inflammation, plasma cells and lymphocytes predominate, the surface epithelium is unaltered, but the gland epithelium is destroyed, at first in patches, later over an extensive area; the thickness of the mucosa may be reduced to a fraction of its normal depth; cysts often occur; regenerative processes are observed. This hyperplasia may lead to *"gastritis chronica polyposa."* A curious metaplasia of the epithelium into a goblet-cell epithelium is frequent.

The second part of Faber's book is called: *"Gastritis and Hyperacidity."* It contains, however, many observations which have nothing to do with the title. At first Faber emphasizes the importance of gastroscopic observations, admitting that he himself is not an expert in gastroscopy, but stating that all gastroscopists unanimously have maintained that the most important result of gastroscopic investigation is the recognition of the enormous frequency of gastritis. He believes that these observations must be accepted because they agree so accurately with the anatomical findings. Hyperacidity often is found in the initial stage of gastritis. At this point Faber starts a discussion on Hurst's "ingenious hypothesis" on the presence of an inborn gastric "diathesis," a discussion frequently reappearing later. It becomes evident that Faber does not accept Hurst's theory although he admits that in the origin of a disease several factors may play some role. In this review the reasons given extensively by Faber shall be omitted. By comparing the anatomical picture with functional findings he makes the following important statements: "There are grounds for stating that no closer parallel between anatomical lesion and functional disturbances exists. Anacidity is certainly a natural consequence in the severe atrophic forms, but, in the less advanced cases, we cannot estimate the degree of secretory disturbance from the anatomical picture, nor even distinguish between cases where the secretion is diminished and those where it is increased." A return of the hydrochloric acid secretion can be observed in all degrees of reduced secretion.

In the following description of the "pyloric gastritis" Konjetznys findings are quoted. Cases are mentioned in which resection was carried where there had been a diagnosis of chronic ulcer, but in which only gastritis was found; this form of gastritis, which causes more or less typical symptoms of ulcer, must be very common. A lengthy discussion of the clinical picture of this disease follows. Hemorrhage is a frequent symptom. Nearly all of these cases have periodic occult hemorrhage, many produce gross hemorrhage. The mechanism of pain, vomiting, stagnation is discussed. It is important to differentiate between erosive gastritis and ulcer because of the different prognosis. The symptomatology in the whole is vague, but, at all events, the great importance of gastritis as the cause of the clinical pictures of dyspepsia must be regarded as established. Faber admits the theory of Konjetzny, that "the disease which leads to chronic ulcer in the first instance must be a gastritis."

The book's last chapter is that on *"Gastritis and Anacidity."* Faber quotes Bloomfield who flatly refuses to accept the thought of gastritis as a cause of anacidity, but also is unable to acknowledge the existence of constitutional achylia. Faber, however, believes that the main argument in favor of gastritis is that when one microscopically examines the mucous membrane of the stomach after proper fixation, one always finds, in patients with chronic anacidity, a diffuse gastritis, tending to atrophy or to pangastritis. "Once one has seen the great inflammatory changes in the mucous membrane in a case of chronic anacidity, one cannot help coupling them with the cessation of secretion." "But it is not our view by any means that all anacidity is due to gastritis." With this Faber arrives at a consideration, long expected by the reader, of the role of psychic influences on the gastric secretion. They are briefly but sufficiently discussed. Also toxins may cause anacidity without gastritic changes, as for example, in Grave's disease. In beriberi and pellagra alimentary factors may have a similar influence. Anacidity in relation to the different age groups then is discussed, the statistics of Vanzant and Alvarez and of Bloomfield are quoted. In children the acid secretion is easily affected by acute diseases, and this probably is due to acute gastritis. Since chronic gastritis may be the ultimate result it can occur at any age. The fact that anacidity so often does not produce symptoms over a long period of time is compared with the periods devoid of symptoms with ulcers and with the initial stage of cancer. Often the inflammation has become "quiescent." However, it is in the nature of pangastritis that it is always advancing, tending toward the atrophic stage. Then Faber considers the relation between chronic gastritis and pernicious anemia and other forms of anemia. He comes to the conclusion that true pernicious anemia must be regarded as a disease of the pyloric organ with deficient secretion of Castle's antianemic factor. In the same way, chronic gastritis is considered to be the

cause of combined cord degeneration. Finally Faber discusses the possibility of chronic gastritis being the primary factor in the development of gastric cancer. Observations are quoted which make the transition of chronic gastritis into gastric cancer likely. However, the author thinks that there must be a tissue predisposition for the formation of cancer.

In conclusion, Faber states that gastritis is not only an extremely common disease, but a very important one. Apart from its own symptomatology, it bears within itself the possibility of chronic diarrhea, chronic ulcer, pernicious and simple anemia, and perhaps cancer. It is in the early stages that we have a prospect of stopping the development of gastritis, and thereby not only relieving the patients of the transient symptoms, but also preventing the further development of gastritis and its often fatal consequences.

It already has been said that this small and inexpensive book contains the results of 40 years' efforts—results obtained against the resistance of almost the entire scientific medical world. Would it be respectful and wise for the present reviewer to critisize in such an exceptional case? Certainly not as far as the many debatable questions arising on each page are concerned; but perhaps it is his duty, as a reviewer, to point to major objections, just because he considers this work as indispensable for the library of every physician who seriously is interested in internal diseases. Only two such objections can be brought forward: (1) The question of the normal histology of the stomach. We have recorded that the normal histology of the stomach is described on but one page, and is based almost entirely on microscopic examinations of the gastric mucosa of young children; there is not even an illustration of the normal antral mucosa. No adult stomach is supposed to be free from chronic gastritis. If this were so, evidently all consequences would lose much of their value. If the changes seen microscopically in the stomachs of adults are considered, three interpretations seem to be possible: (a) every adult, even the healthiest one, has chronic gastritis; evidently with this statement the term of chronic gastritis would lose again its clinical significance; (b) chronic gastritis does not exist; the respective microscopic changes are normal features: this is not credible; the microscopic pictures of complete atrophy cannot be considered otherwise than the consequences of a chronic disease; (c) some microscopic changes in the gastric mucosa of the adult as compared with the microscopic picture as seen in children are characteristic for a "disease" in the clinical sense of the word, others are the "normal" reaction of the gastric mucosa toward the daily hot, cold, or irritant food, or they are the innocuous remainders of acute gastritis. This conception probably will be accepted, and therefore a new demand is made upon the gastroenterologist, namely the necessity of drawing the line between "normal" and "pathological" and to adjust the microscopic with the clinical picture. This new work must be based chiefly on Faber's research; probably it can be carried out only by comparison of clinical with gastroscopic and histologic pictures. (2) The second objection is less important in the principle. Are the specimens obtained at gastric resection useful material; are they beyond criticism as being representative? Does resection in ulcer stomachs sometimes lead to artefacts? It is known that the severe antrum gastritis, as described by Konjetzny, has been considered as a regional peculiarity (Walters), but this explanation is not very satisfactory. When reading Faber's book, one gets the distinct impression that the author himself trusts more to his wonderful formalin injection method than in the microscopic pictures obtained at resection. In this important question only coöperation between the clinician-gastroscopist and the anatomist will lead to a final solution.

However, it certainly has become evident by this latest discussion of gastritis that Faber's book marks a turning point in the history of this particular phase of gastro-enterology.

Rudolf Schindler, Chicago.

Synopsis of Ano-Rectal Disease. By Louis J. Hirschman, M.D., F.A.C.S. Published by C. V. Mosby Company, St. Louis, Mo., 1936, 288 pages. Price $3.50.

IN the Preface, the Author states that "this volume has been prepared in order to bring before the medical student, as well as the general practitioner, a small condensed work on the diagnosis and treatment of the commoner diseases of the anus and rectum." Persual of the book reveals that Dr. Hirschman not only well has attained his goal but, in addition, he has turned out what the reviewer believes really is a model compendium—a needed type of publication in these days of expensive and all-too-often, discouragingly wordy, major text-books in special fields of endeavor.

As we studied this book, the thought forced itself upon us that a useful and profitable opportunity presented itself to the publisher who would issue a couple of dozen such monographs written by practical experts and who had the facilities to enable him to sell them at the modest price asked for Dr. Hirschman's work. But, each book must need be written, actually by a well-recognized authority and each book must be "organized" as practically and efficiently as is this compendium.

Of course, many of us "oldsters" recognize that in many aspects, real *surgical* proctology in the United States almost is symbolical with the name "Hirschman." More than 30 years ago, he was a pioneer in debunking the "touch and go" type of work which passed for "proctology" and in placing on a plane of diagnostic and surgical legitimacy, organic affections involving the anus, rectum and pelvic colon. The road was not smooth, largely because of the obstacles raised by general surgeons who denied—some die-hards still do!—that special surgical manoeuvres were demanded for successful management of ailments in the prescribed field. Only by years of teaching, preaching, skillfully operating and doggedly sticking to his specialty, has Dr. Hirschman demonstrated his major premises. Today, due in great part to him, American proctology is a dignified and necessary specialty, with its own responsibilities, nomenclature, diagnostic criteria, efficient surgery, pathology and earnest, capable proponents. In three decades, our profession has seen proctology advance from semi-quackery, hap-hazard diagnostic methods—and even more hap-hazard and frequently destructive and crippling surgery—to a specialty without whose practice no clinic or hospital can claim first rank. To a scant dozen men—one of whom is Dr. Hirschman—is our profession indebted for such remarkable progress.

The work which the Doctor now puts forth is not just an abstract of his long-recognized and standard,

exhaustive text-book. It is a new and complete publication, systematically, and in orderly and reliable fashion, detailing in easily-read—and remembered—crisp language, the essentials for the accurate recognition and management of crucially-located disease. As a result of many years of undergraduate teaching and operating in important institutions where well-manned laboratories were available to supplement clinical procedures, Dr. Hirschman is uniquely capable of sifting fact from fancy and making worth-while each paragraph of his book.

Although regarded as but a "compend," the book is by no means just a "question-and-answers" publication. Stript of excess verbiage, in 16 chapters, are discussed authoritatively anatomy, physiology, symptomatology, methods of special examination, anesthesia (for both office and hospital employment) and the majority of the functional and organic affections of anus and rectum which will be met in day-by-day practice. Differential diagnosis, pathology and therapy—medical and surgical—are featured. The entire subject is emphasized and made clearer by as many as 174 black and white illustrations and six colored plates. Many of the Author's instruments, dressings, little "tricks" in technique, etc., are exhibited and in numerous instances, photographic reproductions of the actual steps in, and the end-results of, operative procedures make the treatise particularly lucid and valuable. Certainly, we know of few professional directions in which the physician can invest three and one-half dollars and have returned to him so great dividends. This book demonstrates amazingly what of material value can be given when Author and Publisher work in harmony.

Dr. Hirschman's book is printed in particularly well-selected easily-read type, on sturdy paper which brings out values in the pictures, and is strongly and attractively bound. Nowhere does one get the impression of a "cheap" book, even though the price is placed so low. There are convenient chapter synopses and a more than ordinarily complete index.

Probably the reader of this review has secured the impression that the reviewer is well pleased with the work of Dr. Hirschman and Publisher Mosby. Let us add that he *is*, and he feels confident that if the book is bought and is used regularly by physicians generally, better work will be done, patients will be relieved of annoying ailments and, more than at present, will doctors share in the material rewards said to be available by the "prosperity" which trained economists tell us now is inundating the entire land!

Frank Smithies, Chicago.

Marcelo Royer: *Higado y páncreas.* Buenos Aires, 1936.

ROYER has written a very convenient and well illustrated booklet of 132 pages on the liver, bile ducts and pancreas. It is part of a "System of Semeiology." Most of the book is taken up with a discussion of the methods of examination of the liver and bile ducts. I fear that some of the descriptions of these technics are too short to be of service either to a student or to a practicing physician. There is a well illustrated section on the roentgen-ray diagnosis of gall stones. The only criticism I feel like offering in regard to the book is that the author should have had more space in which to go into details. He did remarkably well with the space that he had, but there are many subjects which cannot be treated adequately in a few pages no matter how great the skill of the writer.

Walter C. Alvarez, Rochester, Minn.

Annual Abstracts of Proctologic Literature, 1935-1937

By CHARLES E. POPE, M.D., Evanston, Illinois

PRURITUS

ETIOLOGY AND DIAGNOSIS

Hermance and *Bacon* review all phases of pruritus ani in the Cyclopedia of Medicine.

Zweig believes rectal bleeding comes from ulcerous sphincteric proctitis resulting many times in anal pruritus and eczema. Uses subcutaneous injections of plenocain.

TREATMENT

Cotté reports a refractory case of anogenital pruritus cured by presacral nerve resection and isophenolization of the hypogastric periarterial plexus.

Delherm and *Fainsilber* advocate diathermy in the treatment of pruritus.

Gonzales reports 3 cases of anovulvar pruritus cured by the use of ergotamine tartrate used to provoke a regional vasoconstriction, consequent cessation of vascular serous transudate and edema, and nerve irritation.

Ketron and *Ellis* cite cases and describe the histologic changes in Kraurosis vulae and white spot scleroderma believing that the leucoplacia may be a secondary inflammatory change superimposed on a degenerative vulvar phenomenon. Of 9 cases mentioned 7 were described from a view point of the vulvar pathology. No mention of possible rectal source or relationship was made although the principal case was described as being of marked anal involvement.

Maeth advises the use of anucaine in the treatment of pruritus and fissure. Uses 10 c.c. in 5 c.c. anterior and posterior quadrant injections.

Sulzberger and *Wolf* divide pruritus into idiopathic and secondary types. Advises autohemotherapy, ultra violet radiation and unfiltered X-ray suberythema doses.

Upham reviews the work of others and uses 40% alcohol injections as well as Gabriels solution in the treatment of pruritus.

Cotté, G. and Gaté, J.: (Three Cases of Refractory Anogenital Pruritus Treated Surgically). *Gynecologic*, 34:624, Oct., 1935.

Delherm, L. and Fainsilber, Mme.: (Intrarectal Applications of Diathermy). *Rev. d'Actinol.*, 11:115, March-April, 1935.

Gonzalez Podesta, J. C. and Tordera, A.: (Effect of Ergotamine Tartrate Salve (Gynergen) in Anovulvar Pruritus). *Semana Med.*, 42:122, July 11, 1935.

Hermance, O. W. and Bacon, H. E.: Pruritus Ani. The Cyclopedia of Medicine, p. 1135.

Ketron, L. W. and Ellis, F. A.: Kraurosis Vulvae (Leucoplacia) and Scleroderma Circumscripte. A Comparative Histologic Study. *S. G. O.*, 61:635, Nov., 1935.

Maeth, David: The Injection Treatment of Pruritus Ani and Anal Fissure. *Clin. Med. and Surg.*, 42:392, Aug., 1935.

Sulzberger, M. B. and Wolf, J.: Pruritus and Its Treatment. Med. Clin. North. Am., 19:971, 1935.

Upham, R.: Pruritus Ani. *J. Am. Inst. Homeop.*, 28:541, Sept., 1935.

Zweig, W.: (Diseases of the Rectum). *Wien. Med. Wchnschr.*, 85:1133, Oct. 12, 1935.

STRICTURE

Bacon reviews all phases of rectal stricture in the Cyclopedia of Medicine.

de Brito quotes a case of perforation following simple dilatation of the rectum.

Kondoleon reports two cases of hyperplastic rectal stenosis cured by excision of the infiltrated perirectal tissue by coccyx removed and dissection down to the mucosa, followed by bougie dilatation. Temporary colostomy preceded one of the cases.

Lockhart-Mummery and *Davis* describe a new technique for fibrous stricture of the rectum in which a posterior proctotomy combined with lateral dissection to permit mobilization of the rectum was done. The stricture was divided longitudinally and drained.

Bacon, H. E.: Rectal Stricture. The Cyclopedia of Medicine, p. 1116.
de Brito, J.: (Perforation of Rectum Due to Dilating Strictures). *Rev. Med. Cir. do Brasil*, 43:119, April, 1935.
Kondoleon, E.: (Treatment of Inflammatory Hyperplastic Stenosis of the Rectum). *Zentralbl. f. Chir.*, 1570, July 6, 1935.
Lockhart-Mummery, J. P. and Lloyd Davis, O. V.: Operative Treatment of Fibrous Stricture of Rectum: Description of New Technic). *Brit. J. Surg.*, 23:19, July, 1935.

TUMORS OF ANUS AND RECTUM

(Also see Special Tumors of Colon, Inflammatory Lesions of Colon, Adenomas and Cancer).

Adenomas — (See under separate heading).

Adenomyoma — (See Bowing under Roentgenology and Radium Therapy).

LIPOMA

Weinstein reports what he states is the twelfth case of rectal lipoma. However, *Comfort* has reported 9 cases. It was located in the posterior rectal wall and measured 7 x 4 cm. being attached by a pedicle 6 cm. in length and was covered by a thin mucosal layer slightly ulcerated. Symptoms were of a 6 months constipation and a one day history of protrusion with some pain and bleeding.

LYMPHOCYTOMA

Billaud et al cite a case where tonsillar lymphocytoma was followed in 2 years by rectal lymphocytoma and was cured by roentgen therapy.

Steindl cites a case apparently similar with circumscript hyperplasia of the lymphoid tissue. Surgery is recommended.

MELANO-EPITHELIOMA AND HEMANGIO-ENDOTHELIOMA

Two cases of each condition are cited by *N. D. Smith* and *Broders*. One of each type was found by routine microscopic examination. A hemangio-endothelioma resembled an external hemorrhoid. 330 mgm. hrs. of radium was used. One case of melano-epithelioma died from metastases 21 months later, in spite of irradiation. Hemangio-endothelioma grow slowly, do not necessarily metastasize and have a much better prognosis than the melano-epithelioma where, however, an early diagnosis may cure.

SARCOMA

Del Valle et al and *Chisholm et al* each report a case of sarcoma of the rectum.

Billaud, Brillouet and Viel, A.: (Four-year Cure After Roentgenotherapy of Pure Rectal Lymphocytoma in Same Patient: Question of Metastatic Nature of Second Tumor). *Arch. d'Electric. Med.*, 43:394, Oct., 1935.
Smith, N. D. and Broders, A. C.: Melano-epithelioma and Hemangio-endothelioms of the Anus. *S. G. O.*, 60:74, Jan., 1935.
Steindl, H.: (Bartel's "Rectal Tonsils" and Their Place in Pathology of Lymphatic Apparatus of Rectum). *Zentralbl. f. Chir.*, 62:2594, Nov. 2, 1935.
Weinstein, S. D. and Liberman, W.: Lipoma of the Rectum. *Am. J. Surg.*, 29:424, Sept., 1935.

VENEREAL DISEASES OF THE ANUS AND RECTUM

Clements and *Hughes* state that of 160 patients with genitourinary gonorrhea, 69 showed rectal involvement as determined by culture and microscopic examination. Uses 1:5000 acriflavine efficaciously.

Grandclaude and *Tison* in an extensive study of various acute and chronic infections of the rectum discuss diffuse syphilomas, acquired rectal syphilis, gummas, gummatous ulcerations and sclero-gummatous syphilids. The macroscopic appearances are described.

Simon describes two cases of soft chancre of the anus.

Clements, P. A. and Hughes, K. E. A.: Incidence of Proctitis in Gonorrhea of Females. *Lancet*, 2:18, July 6, 1935.
Grandclaude, C. and Tison, P.: (Rectitis: Anatomico-pathologic Study). *Echo Med. du Nord*, 3:614, April 28, 1935.
Simon, C.: (Non-Infectious Soft Chancre of Anus; Case). *Bull. Med., Paris*, 49:724, Oct. 19, 1935.

CARCINOMA

INCIDENCE AND GENERAL FEATURES

Carcinoma will always continue to be of primary concern to us. The incidence of cancer of the colon and rectum is emphasized by *Balfour* who states that of 833 consecutive cases of carcinoma of the alimentary tract seen at the Mayo Clinic, 25.9% were rectal and 10.9% were colonic. Of this same group in comparison, 11.6% were of the esophagus, 50.3% were stomach, and 1.2% small intestine. The resectability of these growths showed 58% of the rectal group resectible, and 50% of the colon resectible. The colon and rectal cases showed 39% with 5 year cures with resection varying from 36% in the rectosigmoid to 51% in the cecum.

Sheeler states the death rate from cancer has increased from 39 per 100,000 in 1900 to 110.8 in 1932 or a 300% increase. Basing his figures on the 1930 report of the American Society for the Control of Cancer he states 5% were rectal cancers.

Partsch reporting on the incidence of cancer in the large bowel that since the report of Nordmann on German Surgeon's day in 1926, experience with their cases show carcinoma is equally distributed in the large bowel—1/3 in the sigmoid, 1/3 in the left colon and transverse colon and 1/3 in the right half of the colon.

Shaw in one of the papers given in a Symposium before the Iowa State Medical Society states that Mallory in a review of 3535 gastro-intestinal malignancies showed 51.54% were of the large bowel.

As to the exact cause of cancer, of course, nothing has been proven. *E. G. Martin* states "Thoughtful consideration should be given the hypothesis that cancer results from an individual susceptibility to an unknown factor which initiates the pathological process. Heredity however is an unproven factor." That it plays a part in particular types of cancer is stated by Craver as being indisputable, although "in general cancer in man does not appear to be influenced by a genetic factor."

Craver reviews the various exciting factors, the host of irritants, chemicals, tar derivatives and the relation of the latter to the hormones and sterils. He quotes Ewing as saying "Man is the only animal that enjoys unlimited access to food and suffers from restricted opportunity to empty the bowel, and he is the only animal that suffers notably from gastric and rectal cancer." Craver states that with the multiplicity of inciting factors it is questionable as to whether some universal growth stimulating substance will be found operative in conjunction with all factors concerned. Further investigation and advancement may be made as the study and treatment of cancer becomes recognized as a specialty.

Rosser reviews 25 cases of anal cancer studied over a ten years' period and shows that of this series 84% were associated with benign lesions, fistulas 11, hemorrhoids 8, polyp 1, and cryptitis 1, showing that the malignant process was at least partially induced by chronic irritation. Buie's incidence of 1.73% of anal malignancy he believes is explained on the basis of the figure being determined by including total sigmoid as well as rectal lesions, and that only squamous-celled neoplasms were so classified.

Bacon confirms the work of Gruskin which would strongly indicate a genetic factor in the cause of cancer, and advocates this intradermal test as a routine diagnostic measure.

PATHOGENESIS

Junghanns in a study of 130 operative specimens of the colon and rectum states that 70% showed an unquestionable relationship to intestinal polyps. Of those which developed from polyps only 27 belonged to the villous group. These were benign, precancerous or definitely malignant. Epithelial changes occurred in the middle and were fol-

lowed by an ulcer with a hard base when definitely malignant.

Probably one of the most important papers on the pathogenesis of cancer of the rectum is that of *Gabriel, Dukes* and *Bussey* who studied the lymphatic spread by a special method of dissection to determine which cases are of regional lymphatic spread and in which the extension carried up to the point of ligature of the blood vessels. If the latter occurred, extension is usually superior to this point. If a lateral or downward spread occurred, it was a late affair due to hemorrhoidal lymphatic blockage. The lymphatic spread was found regular, not interrupted and ascending along the superior hemorrhoidal artery. 1212 glands were studied from the abdomino-perineal resected specimens.

Larson in an excellent paper reviews the necropsy findings in 210 cases of malignant lesions of the colon both non-surgical as well as 86 surgical. 37% (77) showed no metastases and 113 showed none or only a few glands in the immediate resectible zone. The study shows the older the patient the less likelihood of metastases. The greatest frequency of occurrence was in the two extremes of the bowel, and more than half of the growths could have been visualized by proctoscopic or sigmoidoscopic examination since they were in the sigmoid, recto-sigmoid, and rectum.

DIAGNOSIS AND SYMPTOMATOLOGY

Steindl stresses the diagnosis and recognition of early symptoms of cancer of the rectum. He states Germany and America lead in providing organized clinics for regular prophylactic examinations. Systematic rectal examination in all even slightly suspicious cases should be included in an obligatory plan. He states the need for a low priced proctoscope, the advance in roentgenography oral and enema relief pictures, and air inflation to demonstrate functional and morphologic changes. The earliest symptoms are irregularity of bowel action, and the passage of blood and mucus. Later symptoms, pain, tenesmus, foreign body in rectum occur in varying degrees and combination and are not a dependable symptom-complex.

Shaw emphasizes the early symptoms of cancer of the large bowel. He states that the symptoms and signs of the right half of the large intestine are suggestive but not diagnostic. They may be dull inconstant pain, vague indigestion, anemia, weakness, change in intestinal habit, occult blood, and possibly a tumor mass. Loss of weight and cachexia are late manifestations. On the left side the symptoms are symptoms of complete or partial obstruction, change in intestinal habit, rumbling or visible peristalsis, and a tumor mass revealed by rectal examination.

E. A. Daniels stresses early diagnosis and in a pathological and clinical study of 215 cases found cases divided into 3 classes — mucosal involvement 18%, perirectal tissues invasion but no glandular involvement 35%, and where regional lymphatics were involved 47%. In three years of the three classes alive and well in 60 follow-ups there were respectively 86%, 73% and 19%.

F. J. Smith states many cases of carcinoma of the sigmoid show only gradual increasing constipation until suddenly obstructed.

Moir among cases cited mentions sudden perforation of the sigmoid near its mesenteric border from an obstructive cancer lesion with no preceding symptoms.

Dixon and *Stevens* state in rectal cancer bleeding is the most prominent symptom in 85% of cases and may be the only sign, whereas anemia may be the only outstanding symptom in right colonic lesions.

Raiford reviews and studies 511 cases of carcinoma of the colon and rectum at the Johns Hopkins Hospital from 1900 to 1930. 192 were colon and 319 rectal. The sigmoid and descending colon were most frequently involved in the colon series and the cecum and ascending colon nearly in equal numbers. Medullary and primary mucoid showed the poorest prognosis, and adenocarcinoma with mucoid degenerations, grade one adenocarcinoma, and scirrhous carcinoma gave the best prognosis. Indefinite premonitory symptoms of epigastric discomfort, occasional regurgitation, moderate distention, and change in bowel function are present in the early or slow growing cancer.

OPERATIONS

FIRST STAGE—SECOND STAGE—PERINEAL

In general, opinion favors the two stage operation, and the abdomino-perineal operation is the operation of choice. One stage advocates of the latter advise it for the most part only when the bowel is empty and when the general condition, age and such factors permit it. The perineal resection remains in favor in selected cases and even yet has its advocates to the exclusion of the abdominoperineal.

Morand advocates the perineal or sacral amputation, shows a 50% five year cure and stresses that the operative risk is minimal.

Dixon advocates perineal resection in all cases over 55 years of age, and abdominoperineal only where the general condition and age permit it. He agrees with Lockhart-Mummery that recurrences are most likely in that group where lymphatic node involvement as well as intestinal wall extension are present.

Raiford, judging from his review of cases at the Johns Hopkins Hospital, states that combined abdomino-perineal resection is the method of choice rather than the perineal or sacral, although the operative mortality was much higher in the one stage. 5 year arrests rose from 25% in 1900-1905 to 36% in 1920-1925. In 192 colon cases during the same periods the 5 year arrests or cures rose from 14.6% to 28% and a decrease in postoperative mortality from 31% to 17.3%, whereas the operability increased from 24.1% to 65.5%.

In Germany, *Devist, Madlener, Lexer* and *Naegeli* according to *Taumann* favor the two stage resection, while *Van Haberer* performs a one stage of the colon with a Witzel ileostomy even in cases with ileus.

Finsterer states he differs from Moskowicz who favors a two stage operation of the colon and believes a one stage operation is justified when the intestine is empty, since the mortality is only 12.5% if the operation is carried out under local anesthesia and the sectioned intestine is anastomosed side-to-side. The author reports 132 cases. It is not done as a one stage when acute obstruction is present, but as a three stage resection with side to side anastomosis 1 week after the construction of a fecal fistula. One death occurred in 17 such cases. If the intestine cannot be emptied but there is no acute ileus, choice must be made between a two and three stage operation. In 22 three stage operations, 4 terminated fatally. In the one stage operation on the right and the left side the mortality was 21%.

Partsch states the mortality in one stage and multiple stages in colon cancer is equal, and therefore favors the former.

Yeomans states the one stage abdominoperineal operation of Miles is applicable in 60% of all rectosigmoid cancers and is ideal from the standpoint of wide eradication of the disease and the prevention of recurrences. States the two stage procedure has distinct advantage over the one stage in greater safety and applicability to cases where one stage would be too great a hazard. A rehabilitation of the patient between stages occurs and the lower loop irrigation reduces the inflammation of the injected cancer segment. In selected cases Yoemans advocates perineal resection with anal restoration.

Krause in obstructed right sided colon cases favors a two or three stage operation, otherwise a one stage, and performs an end to side ileocolostomy.

N. B. Anderson favors a two stage Lahey method.

T. E. Jones favors the one stage abdomino-perineal operation and cites 135 cases with a mortality of 11% which he believes compares favorably with the two stage if the mortality of the two operations were to be included. The percentage of immunity from carcinoma over 5 years is 52%, over 3 years 62% and 67% for any time less.

Rankin advocates the two stage Miles operation inasmuch as the one stage offers too formidable a risk to most patients. Mummery operation with colostomy and posterior resection he believes too limited a glandular removal. The Jones operation is a satisfactory procedure but the loop colostomy sometimes leaves a mucus fistula posteriorly. Of 300 cases colon and rectal cancer previously reported 13% were grade I, 58% grade II, 21% grade III, and 8% grade IV. The operative mortality stays at 10%, and one or two stage abdominoperineal resections of 99 cases the last 4 years has been 8% with operability at 60%. Whereas the operative mortality is 5% in posterior resection the 5 year results in 300 cases show only a 38% 5 year cure as compared to the one stage Miles 3 year cure of 79%.

Several new points of surgical technic have been published.

Trueblood submits an abdominoperineal operation that requires two operating groups—one for the abdomen and one group for the anus and perineum. The patient is placed in the lithotomy position with the table tilted in Trendelenburg. Each group facilitates the other.

MacGuire performs a preliminary cecostomy and may even delay operation for 2 months if necessary to prepare the patient generally. The operation is performed then as a one stage abdominoperineal resection. After dissecting to below the peritoneal reflection the abdomen is temporarily closed and the perineal resection done in the lithotomy position, the lower segment covered with a rubber glove, the abdomen reopened and the resection completed.

Devine basing his operation on experimental work in animals where isolated colon loops are found bacteria-free, does a transverse colon division and bring the ends to the abdominal wound margin. Resection follows some weeks later. Six months later the rectal stump in the rectosigmoid resection is united to a mobilized sigmoid by telescoping the latter into it. The colonic segments are reunited and the artificial anus is closed in the usual Mikulicz fashion.

MIKULICZ PROCEDURE

The Mikulicz procedure and its modifications and mobilization and transposition operations of the colon received considerable attention.

Moskowicz advocates a return to the Mikulicz 4 stage resection which should include the mesocolon and its glands, should include a suturing of the efferent and afferent loops uniting them on the mesenteric site for a distance of 10 cm. or the distance to which the enterotome is to be applied. The closure may be improved by cauterizing the mucosal aspect to retract the stoma inward and close it extraperitoneally. The procedure reduced von Mikulicz' mortality from 50% to 12.5% whereas the one stage resection advocated by Nordmann carries a mortality of 33%, in the large clinics notwithstanding. Advocates loop limb suture and the pacquelin cautery to the colostomy stoma to narrow the size.

OTHER CONSERVATIVE AND EXTERIORIZATION METHODS

There is quite a marked tendency towards more conservative measures in operative procedure on the colon and rectum. Apart from the Mikulicz procedures which is again brought to the fore are operations devised to gain asepsis through exteriorization methods.

An outstanding paper is that of *Koster* who advocates resection of either the right or left colon by means of a loin incision and a retroperitoneal approach. Abdominal exploration and anastomosis of the bowel is done as a preliminary procedure. Advantages gained are through wide exposure and lymphatic excision and extraperitoneal plantation of the divided limbs of the colon.

Collins combines an obstructive resection with a Mikulicz clamping of an intended spur of the remaining limbs of a resected right colon, but adaptible to other portions of the colon. The usual intra-abdominal peritoneallization and drainage is done. Preliminary cecostomy decompression is avoided.

Goldschmidt quotes 7 cases of chronic inflammatory tumors responding to laparotomy and drainage.

Dixon describes two cases of previously resected sigmoids where mobilization by separation of the outer leaf of descending colon peritoneal reflection permitted bowel restoration.

Preliminary decompression to surgical resections of the colon is urged by *Krause* who advocates Witzel ileostomy, *MacQuire* who describes an original permanent ileostomy, and *Glenn* who advocates transverse colon colostomy.

COLOSTOMY

Best and *Hicken* describe a plastic operation for the cicatrized and retracted colostomy which prevents stenosis recurring by mucosal suturing and elevation of the colostomy and suturing to a surrounding rubber doughnut.

Landsman describes the post-operative care of the colostomy and advocates the use of a rubber spool as an aid to fecal control.

Warwick discusses the colostomy faults and complications and describes a colostomy wherein fascial suturing by external oblique or thigh transplant through a holed incision is done.

Dixon advocates colostomy in debilitated patients for cancer of the upper sigmoid followed by later abdominoperineal resection.

Nobuoka describes 3 cases where he adapts the Kurtzahn's method for constructing a closable anus.

THE CONSERVATIVE OPERATION

The conservative operation for sphincter control has aroused considerable discussion and has its staunch advocates.

Breitkapf reports a consecutive series of 19 cases where sphincter preservation following rectal resection was obtained. Besides the pull through method of Hochenegg and the circular suture according to the Küttner method, the operation used was with anal mucosa resection both with or without sphincter division.

Turner reported 19 such cases before the British Royal Society of Medicine. Colostomy preceded only 6 of the 19. The operation is suitable in only 5% of all cases coming to surgery. There was but one death. Gabriel in discussing his paper states only 11% or 16 cases of those operated upon at St. Mark's Hospital. He did not favor it. Neither did Lockhart-Mummery. Sir Gordon Watson favored it where large papillomata are involved. Rayner described a modified Hochenegg procedure.

Mandl describes and advocates his modified Hochenegg procedure and states that though this "extended sacral operation" is not suitable for all operations, other operative measures may be permissable such as endorectal electrocoagulation and linear rectotomy.

Steindl agrees with Mandl that such an operation is advisable in certain cases and believes the radical removal of pararectal tissue is the point par excellence.

Gold and *Stritko* advise the Mandl operation but state high lying tumors require abdomino-perineal resections and that a narrow pelvis and such causes are contra-indications for the Mandl operation. State the abdominoperineal operation has come into disrepute because of its high mortality.

CARCINOMATOUS INVASION OF THE COLON

A very unusual case is reported by *Lawrence* and *Steele* where an infiltrating carcinomatous ulcer of the stomach located 2 inches from the pylorus was found to have secondarily invaded the rectum, the cecum and ascending colon, and the splenic flexure. All had diffuse thickening of the wall and associated constriction of the lumen.

Duval describes his technic for gastrectomy and colectomy for neoplasm of the stomach with adherence to the transverse colon.

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COLON

CHRONIC ULCERATIVE COLITIS

(Idiopathic Ulcerative Colitis—Non-Specific Ulcerative Colitis — Bacillary Dysentery).

BARGEN'S DIPLOSTREPTOCOCCUS

Bargen has published a book on "The Management of Colitis" in which in addition to covering the various colitides in detail especial emphasis is given to chronic ulcerative colitis.

Bargen and *Kemble* review in careful detail the predisposing factors in 20 cases of chronic ulcerative colitis.

Brust and *Bargen* reviewing 1291 cases seen at the Mayo Clinic between 1924 and 1932 found only 25 or 1.9% over 60 years of age. Of these 25, 16 were males and 9 females. None had polyps, one had carcinoma of the bowel. All but 2 cases responded very well to vaccine therapy. 20 were greatly improved in 2 weeks.

Bargen and *Dixon* review 25 cases of carcinoma and 2 cases of lymphosarcoma of the colon associated with chronic ulcerative colitis. Conclusions drawn are that in the younger individual the condition likely will be fulminating and multiple and that vaccine therapy is decidedly indicated.

Gallart Mones and *Domingo* from a bacteriologic study of 25 cases conclude that although the Bargen and Buttinux organisms are frequently found they resemble streptococcus mitis on the one hand and streptococcus saprophyticus on the other and are not in their opinion specific. In the rabbit ordinarily non-virulent organism are virulent when obtained from ulcerative colitis patients.

Hare in his presidential address before the Royal Society of Medicine discusses ulcerative colitis. States that Hern found 50% of his cases benefited through the use of Bargen's vaccine. Although Hurst reports good results with antidysenteric serum the author could not substantiate the same in his own cases. Clinically no substantiation could be given by the author to the experimental work by Cramer with Vitamin A and McCarrion with vitamin B. The author reports a macrocytic type of anemia in an ulcerative colitis case that responded to liver therapy.

Howe reviews 20 cases seen in 6 years treated with autogenous vaccine, brewers yeast, haliver oil or vitamins and the usual dietary management. 30% are well, 35% markedly improved, 15% moderately improved, and 20% died.

Radner cites 16 cases and treated 8 cases with the autogenous Bargen diplostreptococcus vaccine, with remarkably good results in 5 cases. 2 additional cases showed an associated endomoeba histolytic, and 2 the streptococcus hemolyticus.

B. DYSENTERIAE

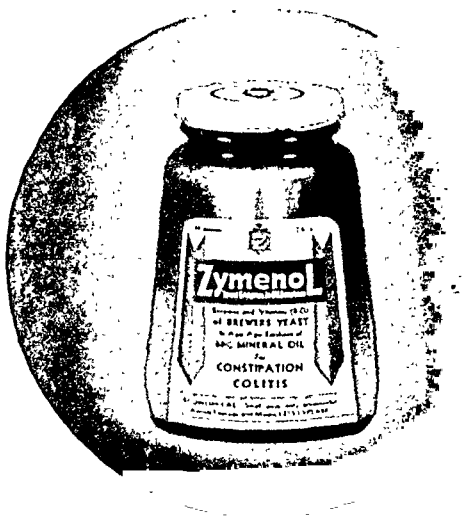
Crohn and *Rosenak* in a review of 90 cases where mainly through the use of polyvalent anti-dysenteric serum given intravenously, and associated treatment such as acriflavin retention enemas, diet and the usual medicinal measures state 44.5% were cured, 30% improved and only 10% not improved. The authors are enthusiastic over Bargen's fine therapeutic results but do not accept the diplostreptococcus as being the proven cause of this disease.

Felsen reports an acute form of bacillary dysentery in 3 cases characterized by rapid course progressive leucopenia with granulocytopenia and fatal termination. He believes an enteric and neurotropic toxin is present, a virus causing the latter and urges early diagnosis and immediate dysenteric antitoxin. Two of the cases showed ulcerative enterocolitis and polyposis of the distal ileum and entire colon. Felsen regards chronic ulcerative colitis and regional ileitis as varied forms of bacillary dysentery.

Hurst has advocated the use of polyvalent antidysenteric serum since 1920 which he advocates at an early stage to prevent chronicity and gives in daily doses intravenously. He believes

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chronic ulcerative colitis due to the dysentery bacillus or an allied parenteric organism.

Winkelstein advises antidysenteric serum and bacteriophage in nonspecific ulcerative colitis obtaining positive agglutinins in 22% of such cases, and a bacteriophage potent against one or two of the strains of the b. dysenteriae in 36% of cases.

OTHER ORGANISMS

Arrese and his co-authors observing their cases for 3 years state good results followed the use of various vaccines in 22 cases. The diplostreplococcus of Bargen appeared to be identical with the enterococcus type B of Gundel and they do not believe it specific. The organism from 29 cases of ulcerative colitis cases were studied. Anaerobes particularly in Cl. perfringens variety were always found in intestinal ulcers.

Dack, Heinz and *Dragstedt* were able to produce complement fixation tests in 4 patients with chronic ulcerative colitis with antigen prepared from isolated loops of patients and from 3 experimental monkeys, using anaerobic flora which was non-spore forming and gram-negative. Similar strains were recovered from two monkeys recently recovering from the Flexner type of dysentery. The flora closely resembled bacteroides fragilis and fundiliformis actinomyces necrophorus, and the bacillus necrophorus.

MIXED VACCINE

Gesterlin and his co-authors cite good results in treatment in 15 cases where a staphylococcus, streptococcus and b. coli antivirus was used daily.

Reye reports excellent results in 6 cases using b. coli cultures from normal individuals as a retention enema, the same mixed in glucose solution.

DEFICIENCY STATES

Mackie and *Henriques* found deficiency states present in 47 of 75 cases as seen in oral mucosal changes, anemia, blood chemistry changes, and peripheral neuritis. Mackie and Pound found on further roentgenographic study disturbances of motility and such which the deficiency states could have caused by affecting the small bowel.

CALCIUM THERAPY

Haskell and *Cantarow* report on further good results by calcium and parathyreoid treatment.

Klinefelter advocates calcium therapy with high vitamin diet.

HEMOSTATIC TREATMENT

Hetenyi treats with ascorbic acid basing the effect as due to the hemostatic effect with the accompanying vitamin C deficiency on the part of the patient.

Kochs and others state pectin treatment has given good results by reason of its hemostatic effect.

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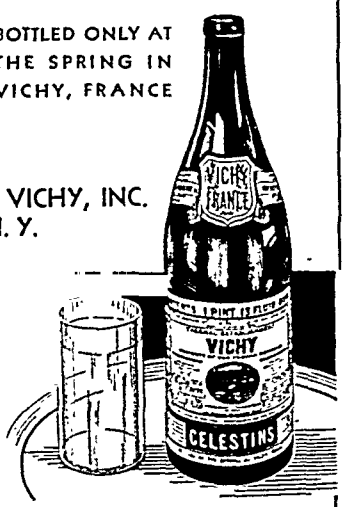
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THE IRRITABLE DYSFUNCTIONING COLON, CHRONIC COLITIS, OR UNSTABLE COLON

Numerous papers touch upon this subject but do not confine their subject matter to it, generalizing upon tumor growths or discussing this disease in the differential diagnostic consideration of other colopathies. Valuable and interesting contributions however have been made on the subject which include consideration from the biochemical, vitamin deficiency, allergic, psychic, emotional motor and secretory dysfunction, vagotomic, reflex, toxic and radiologic aspects.

GENERAL

Gallart-Mones states that only a few of the colitides should be termed colitis. In reviewing 40 cases the dysfunction present was general, not connected with secretory insufficiency, metabolic disturbance, or hereditary factors, was suggestive of hypersensitivity, showed colonic hyperkinesis, and required individualized treatment. States these cases are pseudo-colitis.

Hurst speaks of the unhappy colon, describes the normal and pleas for sane gastro-intestinal hygiene, freedom from bowel irritants and shows how many concepts are based on erroneous anatomic and physiologic teachings.

Laus in an extremely informative paper reviews the essential colonic physiology, details the normal and abnormal stimuli and gives a comparative clinical interpretation based on numerous case studies.

ALLERGY

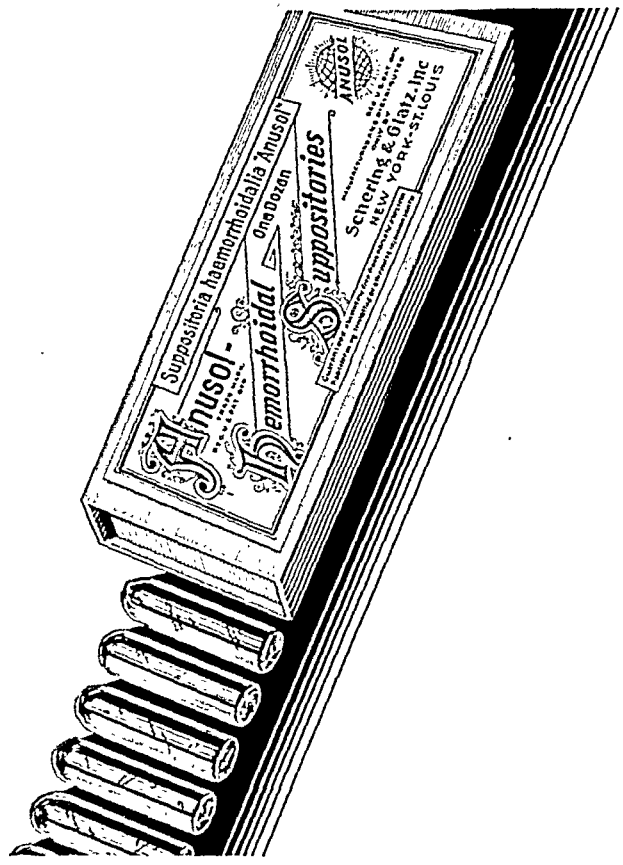
Alvarez states that digestibility of foodstuffs varies with individual susceptibility and that food sensitivity should not be laid totally to allergic sensitivity.

Wiltsie states that he disagrees with Alvarez and states that all symptoms of which a patient might complain seem to be due directly or indirectly to intestinal toxemia. Advocates mainly colonic irrigation.

Hare states that 85% of 38 patients had a personal or family history of allergy and considers that factor as important and is in accordance with Pearson's findings in 1933 where 26% of generally healthy adults show the same. Moore stresses the same.

BIOCHEMICAL

Trumper as a biochemist writes a very interesting paper and discusses the need for restoring acid-base equalibrium in the dysfunctioning colon to replace the lost minerals and to restore the proper alkali deficiency. States that colitis manifested by diarrhea not only rids the bowel of irritating substances, but also depletes it of necessary minerals, inorganic constituents and enzymes thus producing putrefaction, irritation both physical and



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chemical, nervous instability, primary and sometimes secondary dehydration, and severe acidosis.

NEUROGENIC

Bodman cites 7 cases and believes that in most ulcerative colitis is a terminal stage of colon dysfunction of psychogenic origin.

Davis, Sullivan and *Young* plea for the recognition of neurogenic and psychic factors in colitis.

Morgan stresses the viscero-motor and viscero-sensory symptoms as frequently manifestations of a general body state. Classifies colitis as mucus, granulosa, atrophicans, hemorrhagica and ulcerative colitis.

REFLEX GASTRO-INTESTINAL

Bergeret and *Caroli* review 100 cases where chronic appendicitis caused colitis as was determined by appendectomy.

Feldman stresses the associated hyperirritability and hypermotility of the right colon with appendiceal abscess.

Mocnch in an excellent paper cites the various gynecological conditions that may give rise to gastro-intestinal symptoms and ascribes this to factors such as anatomical interrelation of blood supply, general and autonomic nervous innervation, as well as related factors of a mechanical, chemical and toxic nature.

DIETARY

Fitts describes a syndrome seen in 85 cases with B. avitaminosis with gastric atony, spastic colon, low hydrochloric acid, and mild hypothyreoidism responding to dietary measure with wheat germ.

MELANOSIS

Zobel and *Susnow* found an incidence of melanosis of 3.5% in 200 cases examined. Constipation was present and cascara sagrade was habitual.

METADYSENTERY

Castellani reports a form of colitis due to b. ceylonensis A. and B. (Castellani 1907) and b. madampensis somewhat similar to the dysentery bacillus termed metadysentery. It is characterized by recurrent dysentery with long periods of remission. Geographically it is tropical to temperate in distribution.

VACCINE

Mateer and *Baltz* in a brilliant paper discuss the results obtained in the treatment of non-ulcerative colitis or the unstable colon. 1000 cases treated during the last 4 years. 3000 cases showed skin sensitivity. The therapy was found to be a distinct value in obstinate cases as well as a valuable adjunct in the usual run of cases with chronic functional diarrhea, chronic "toxic vertigo" and chronic headaches.

Tripodi cites the results of intravenous antigonorrheal vaccine treatment in 60 duodenal ulcers and 40 chronic colitis cases with benefits marked in the former but uncertain in the latter and due to the relaxation of the smooth musculature of the bowel.

DIARRHEAS IN INFANCY AND CHILDHOOD

Terrell and *Owen* report an epidemic occurring near Fort Worth, Texas, effecting thousands of adults but predominantly infants and children. All cases showed a predominating large gram-positive diplostreptococcus. 14 cases were negative to agglutination for the various dysenteries and typhoid. Autopsies revealed a hemorrhagic mucosa and lymphoid hyperplasia with superficial ulceration with cultures showing the same organism. Rabbit inoculation caused mucosal congestion, large amounts of mucus and bloody mucus but no ulcerations.

Johnston and *Kaake* describe an epidemic in the nursery of a small Toronto Hospital where in 15 cases involved, 9 deaths occurred, due apparently to b. dispar. Reports two previous epidemics one of 1931 and one of September, 1934, due apparently to b. dysenteriae (Sonne).

Loeschke shows that in severe toxic dysenteries in childhood severe toxicity

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2. UNIFORM SUSPENSION

Horlick's colloidal constituents, notably the dextrins and gluten derived from malted cereals, and the albumin of the milk, make for uniform dispersion—a stable suspension, and shadow of even density.

3. EXPULSION TIME

Well within normal limits.

4. PENETRATION

The barium meal prepared with Horlick's penetrates the gastro-intestinal tract throughout. Unlike meals which must be given cold to disguise degree of acidity, Horlick's may be given at body temperatures. Thus it will not disturb correct stomach motility, make diagnosis less certain.

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Horlick's does not lump or constipate.

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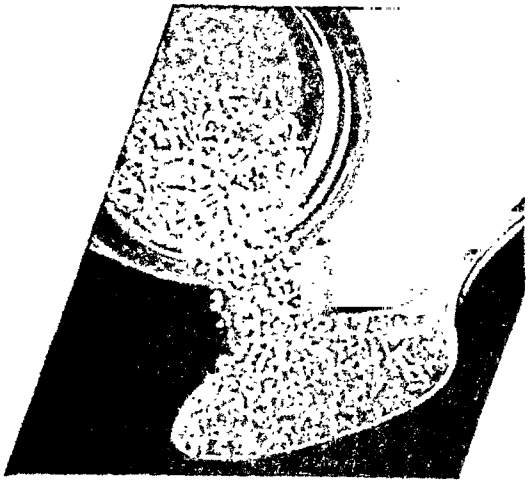
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and dehydration are the predominate factors.

Melgaard in referring to the treatment of diarrhea in infants and children stresses the need for opiates, diet, and the prevention of cross infection.

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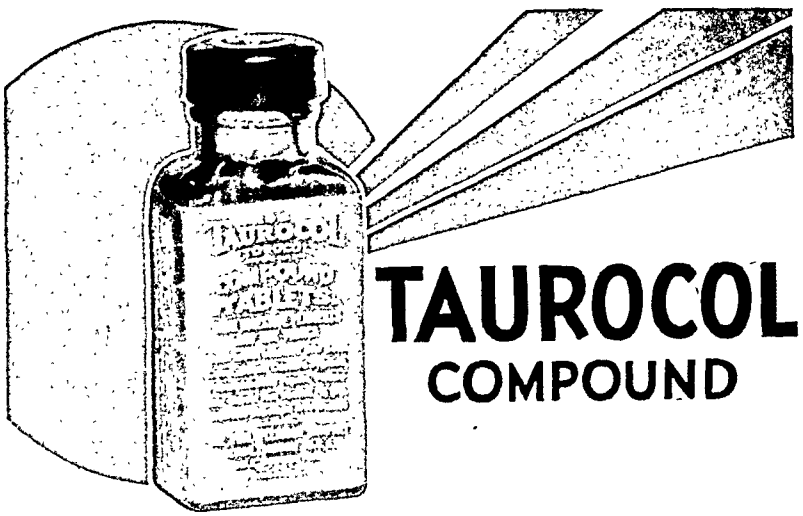
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DOLICHOCOLON

ETIOLOGY AND PATHOLOGY

Bernard believes that dolichocolon is postembryonic due to an anatomical-clinical entity leading to a disturbance of motility by reason of an anomaly of fixation or length of mesentery.

Blanco reviews the theories of origin and classifies according to sigmoid, descending or transverse, demonstrating cases in children with radiograms.

TREATMENT

Seneque and *Milhiet* describe a one stage exteriorized anastomosis.

Nard describes a technique which by a lateral Trendelenburg position and a transverse incision permits better exposure.

Bernard, A. and de Tayrac, A.: (Dolichocolon; Pathogenic Study). *Gaz. d. Hop.*, 108:861, June 22, 1935.

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INFLAMMATORY LESIONS OF THE COLON

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ileitis or chronic cicatrizing enteritis is reported by *Erb* who reports 4 cases with pathology limited to this region characterized by edema, congestion, lymphoid tissue inflammation, necrosis and symptoms of severe prostration and characteristic of appendicitis. He states that these cases were similar if not actually the same as those described by Crohn et al, Harris, Bell and Brunn.

A similar case is reported at the Cabot Clinic.

Felsen reports a summary of evidence which he has accumulated in support of his contention that bacillary dysentery, distal ileitis, and non-specific ulcerative colitis are different stages or manifestations of the same disease.

INFLAMMATORY LESIONS

Brücke reports a case of ischemic stenosis of the transverse colon 11 days after ligation of the middle colic artery.

Hardt reports an unusual case of emphysema of the cecum. No cause was found and the cultures from the air blebs were negative.

Bargen, J. A. and Dixon, C. F.: Regional Ileitis. *Proceedings of the Staff Meetings of the Mayo Clinic*, 10:814, Dec., 18, 1935.
Brücke, Hans V.: Ueber Ischämische Darmstenose. (Ischemic Stenosis of the Intestine). *Arch. f. Klin. Chir.*, 182:95, March 4, 1935.
Erb, I. H. and Farmer, A. W.: Ileocolitis: Acute Ileocolitis Simulating Appendicitis and Characterized by Edema of Ileocecal Region and Mesenteric Glands; Its Relation to "Regional Ileitis" or "Chronic Cicatrizing Enteritis." *S. G. O.*, 61:6, July, 1935.
Hardt, L. L.: Emphysema of the Cecum. *J. A. M. A.*, 105:1982, Dec. 14, 1935.

MECHANICAL AND TRAUMATIC CONDITIONS OF THE COLON

Cunniffé reports an intussusception of a cancer of the descending colon treated successfully by Mikulicz operation and diagnosed pre-operatively by X-ray.

Hardouin reports 4 cases of volvulus of the sigmoid and advises immediate resection if possible in all such cases.

McClure reports a case of torsion of the entire small bowel with symptoms of persistent constipation, umbilical pain, meteorism, vomiting, etc.

Saeltzer and *Rhodes* report 5 cases where terminal colon lesions resulted in diastasic perforation of the cecum.

Vanlande reports volvulus of the pelvic colon in 2 cases.

Walkling reports a ruptured sigmoid in a 60 year old male due to inserting a brass nozzle sprinkler into the rectum in the attempt to give an enema.

(See also congenital anomalies and dolichocolon).

Cunniffe, E. R.: Double Echinococcus Cyst of Liver Intussusception of the Descending Colon. *Ann. Surg.*, 101:1447, June, 1935.
Hardouin, P.: (Four Cases of Volvulus of the Sigmoid Colon). *Bull. et Mem. Soc. Nat. de Chir.*, 61:225, 1935.
McClure, H. M.: Volvulus: Torsion of the Whole Mesentery. *J. Oklahoma State M. A.*, 28:100, 1935.
Saeltzer, D. V. and Rhodes, G. K.: Diastasic [illegible] of the Normal Cecum, Resulting [illegible] Colon. *Ann. Surg.*, [illegible] of Pelvic Colon; 2 Cases). *Bull. et Mem. Soc. Nat. de Chir.*, 61:1030, Oct. 26, 1935.
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MEGACOLON

ETIOLOGY AND PATHOLOGY

Freeman states that whereas some maintain rectosigmoidal spasm is responsible for megacolon, the trouble is mainly due to sympathetic and parasympathetic unbalance inasmuch as lumbar ganglionectomy improves the condition. Believes sphincter spasm may lead to megacolon and frequently accompanies the pathology.

Zander describes a case necessitating right colon resection that came by reason of previous surgery for constipation where an exclusion of the colon had been done.

Pitman describes a case where dilatation and stasis of the proximal colon came secondarily to a napkin ring defect just above the cecum as well as because of the added pathology of herniation of the stomach.

Caciro describes a valvular megasigmoid originally described by Riedel and Perthes which showed a fecalith of enormous size at 16-17 cm. distance from the anus in the megasigmoid where a true spur was found and behind it the base of the cavity.

TREATMENT

Hueck believes in surgical resections in certain selected cases.

Orator states the need for individualization in treatment and cites three cases to demonstrate his point. One case he states showed a congenital maldevelopment of the sacral parasympathetic nervous system and would respond to lumbar sympathectomy, but another case cited seemed to indicate a pathological overstimulation of the parasympathic nerves and by this procedure would be made only worse.

Rankin reports 10 cases operated upon. Favors inferior mesenteric presacral nerve section. 7 cases were for congenital idiopathic Hirschsprung's Disease and 3 for constipation. Believes that the aorticorenal or renal periarterial plexus is joined by the branches of the first and second lumbar ganglions to form the intermesenteric plexus so that lumbar ramisectomy and ganglionectomy may affect the descending colon, sigmoid, rectum and internal sphincter by reason of the innervation to colon and rectum.

Dominici favors expectant treatment and surgical treatment only if this fails.

Rives and *Strug* report that a case reported previously with S. J. Stabins where spinal anesthesia was used therapeutically has remained well for 4 years. Refer also to good results obtained in another patient with megacolon and two patients with obstinate constipation so treated and reported by these co-authors in January, 1935. The

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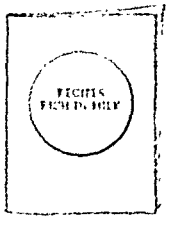
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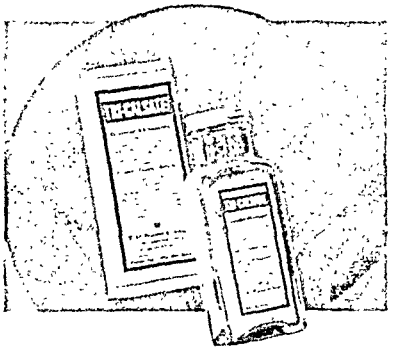
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present report concerns two cases one 8 years of age and one 9 years of age with excellent results in the first and partial in the second. 75 to 100 mgm. of novocaine was used. It is thought that this anesthesia isolated the colon from its central autonomic control and thereby permits normal function.

Caciro, J. A.: (Valvular Megasigmoid with Fecal Mass; Colectomy in Two Stages). *Bol. y Trab. de la Soc. de Cir. de Buenos Aires*, 19:158, May 8, 1935.

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Zander, P.: (Formation of Megacolon Following Anastomosis of the Large Bowel Because of Chronic Constipation). *Zentralbl. f. Chir.*, 62:638, March 16, 1935.

PHYSIOLOGY OF THE COLON

Very valuable contributions were given to our specialty in this field of research.

FECES

Pachioli and *Mengoli* by a colorimetric study of the stools of 381 children states that breast fed infants stools are acid showing a p.h. of 5.6, that the p.h. value varies with the diet and that after 2 years of age the stools are alkaline and not influenced by diet.

Goiffon has published a manual describing the normal formation of feces, the examination, evaluation and the therapeutic considerations of fecal examination for clinical purpose.

Amalfitano in two separate articles describes an acetic acid test for albumen which is indicative he states of intestinal ulceration, and studied the presence of amylase in 24 cases claiming an increase in chronic inflammatory intestinal disorders and a decrease in the acute.

Boas and *Häcker* in separate articles attempt to evaluate the Boas test of feces and state the presence of unchanged hemoglobin and copratoporphyrin signifies the suspicion of cancer.

Ehlert and *Fetwurst* state a greatly reduced value of urobilinogen is highly significant of cancer present below the cardia 27 of 31 cases of carcinoma having fecal values indicating cancer.

Steggerda found in the study of feces in humans and dogs that the rectal end is 10% more concentrated than the colon end, and that the proximal colon is 10% more concentrated than the cecum, which he believes is directly related to the proportionate degree of vascularity of those portions of the bowel.

THE NERVOUS MECHANISM CONCERNED IN COLON FUNCTION

Kobat, Anson, Magoun and *Ranson* experiments are a distinct contribution. By faradic stimulation of the lateral hypothalamic area in the unanesthetized cat they produced the same sympathetic response described by Cannon in his emotionally excited cats and produced an inhibition of gastro-intestinal motility. The supramamillary commissure produced the same results suggesting this to be an afferent pathway to the gut.

M'Fadden, Loughridge and *Milroy* studied one or more of the nerve pathways to the distal colon and observed the effect upon the colon motility following severance. Interruption of sympathetic pathways leads to sphincter relaxation and an atonic dilated colon. Section of the pelvic nerves or dornal sacral roots caused a hypermotile colon and spastic sphincter.

Denny and *Graeme* described and studied the reflex act of defication finding that the sacral segments of the cord cause greater fusion of rectal contractions, whereas the sympathetic nerve supply through the hypogastric to the anus and rectum does not. The mechanism of defecation depends upon the reaction of the rectum to distention. Automatic and reflex responses come also from cutaneous area of sacral segments.

Arendt on the basis of radiologic study states the junction of the first and middle third of the transverse colon constitutes the Cannon-Böhm point which is the point of change from upper splanchnic innervation to the lower innervation of the vagus and the pelvic plexus.

Kolossow and *Polykarpowa* by sectioning the hypogastric nerves found that the sympathetic nerves of the rectum are postganglionic fibers of the same nerve elements present in extramural ganglions and that the fibers are actually axon ganglion cells.

MOTILITY CHANGES IN THE COLON

Kreuzfuchs states that the capacity of the colon is necessary information to interpretation of the mechanism of evacuation.

Sparks and *Colins* working on rats with carefully controlled diet and control series substantiate the work of Hargreaves, Fletcher and Dickson, and show that the volume of the colon if maintained on a diet deficient in vitamin B increased strikingly.

Okae found a direct relationship between peristalsis and increased circulation of blood in the bowel wall. The effect of numerous drugs were studied in this respect. Peristalsis was definitely effected by pituglandol, esserin, prostigmin and barium chloride.

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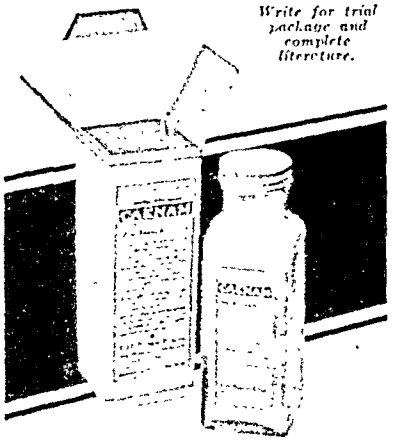
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proctoscopic cadaver, and laparotomy examination describes the approximation of the mesenteric and antimesenteric rectosigmoid walls as due to circular muscle contraction, and the descent of the antimesenteric wall due to intra-abdominal pressure.

Arendt, J.: (Significance of Cannon-Boehm Point in Functional Movements of the Colon). *Fortschr. a. d. Geb. d. Roentgenstrahlen*, 51:508, May, 1935.

Denny, Brown and Graeme, R.: Nervous Control of Defecation. *Brain*, 58:256, Part 2.

Goldman, C.: Normal Excursion of Sigmoid into Rectum. *M. Rec.*, 142:188, Aug. 21, 1935.

Kabat, H., Anson, B. J., Magoun, H. W. and Ranson, S. W.: Stimulation of Hypothalamus, with Especial Reference to its Effect on Gastro-intestinal Motility. *Am. J. Physiol.*, 112:214, May, 1935.

Kolossow, N. G. and Polykarpowa, G. A.: (Experimental Morphologic Investigation of Autonomic Innervation of Rectum). *Ztschr. f. Anat. u. Entwicklungsgesch.*, 104:716, 1935.

Kreuzfuchs, S.: (Mechanism of Evacuation of Colon in Relation to Its Capacity. *Roentgenpraxis*, 7:302, May, 1935.

M'Fadden, J. S., Loughridge, J. S. and Milroy, T. H.: The Nerve Control of the Distal Colon. *Quarterly Journal of Experimental Physiology*, 25:315, Dec., 1935.

Okae, K.: Reciprocal Relationship Between Intestinal Motility, Blood Circulation in Intestinal Wall and General Circulation. *Mitt. a. d. med. Akad. zu Kioto*, 14:665, 1935.

Sparks, M. I. and Colins, E. N.: Role of Vitamin B. in Tonus of Large Intestine. *Am. J. Digest. Dis. and Nutrit.*, 2:618, Dec., 1935.

Special Tumors of the Colon Other Than Adenomas

Bartlett reports a case of endometrial tumor of the intramuscular portion of the sigmoid bowel wall, thought by the author to be embryonal.

Böhm reports a lymphatic cystoma of the descending colon.

Geschickter reports 178 cases of benign tumors with the following incidence:

	Total	Colon	Rectum	Retroperitoneal
Adenomas	90	10	55	
Argentaffine tumors	36	2		
Enteric cyst	1			1
Myomas	24		1	
Angiomas	6		1	

Konjetzny reports 2 cases of endometriosis of the lower segment of the sigmoid, one confined to the longitudinal muscle layer and one penetrating the entire muscular layer.

Melicow cites four cases of xanthic lesions one of which was of the cecum and ascending colon due to kidney sinus. The xanthic change is due to excess of lipoids on the basis of lipogenic response by cells of the reticuloendothelial system.

Varner reports a sigmoid myoma successfully removed by two stage resection.

Bargen and *Dixon* review 2 cases of lymphosarcoma of the colon.

Bargen, J. A. and Dixon, C. F.: Chronic Ulcerative Colitis with Associated Carcinoma. Progress in Management. *Arch. Surg.*, 30:851, May, 1935.

Bartlett, R. W.: Endometriosis of Sigmoid. *Am. J. Surg.*, 29:122, July, 1935.

Böhm, G.: (Lymphatic Cystoma of Wall of Descending Colon). *Arch. Ital. d. Mal. d. App. Diger.*, 4:250, July, 1935.

Geschickter, C. F.: Tumors of the Digestive Tract. *Am. J. Cancer*, 25:130, Sept., 1935.

Konjetzny, G. E.: (Heterotopic Endometriosis of Large Intestine). *Chirurg.*, 7:279, May 1, 1935.

Melicow, M. M.: Xanthic Lesions. *J. A. M. A.*, 105:768, Sept. 7, 1935.

Varner, H. H. and Green, J. L., Jr.: Myoma of Colon. *Southwestern Med.*, 19:218, June, 1935.

Congenital Anomalies

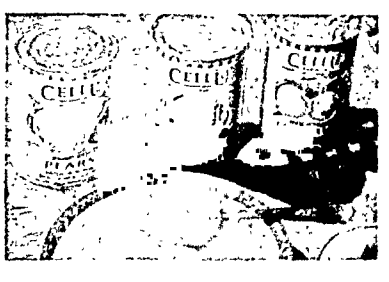
There is a considerable number of case reports covering imperforate anus, vestibular and vulvar anus and congenital anorectal atresia.

Klinefelter reports a completely absent colon in an otherwise normal newborn. *Patel* reports a case showing total atresia in a 57 year old adult with symptoms present since 15 years of age interpreted as doubtfully congenital but with congenital disposition towards atresia.

The omentocolic membrane and the ligaments of the right colonic angle are discussed in reference to intestinal obstruction.

A large number of cases are reported where with abnormal rotation cecal volvulus occurred due to mobile ileum, and cecum with inverted cecum, and other anomilies of ileocolic fixation. *Consiglio* states many asymptomatic cases of mobile cecum occur and in most cases of acute appendicitis may be a predisposing cause.

Sweet reviews acute and chronic volvulus of the cecum from the records of the Massachusetts General Hospital from 1873 to 1930. Exclusive of strangulated hernia 7 cases are re-

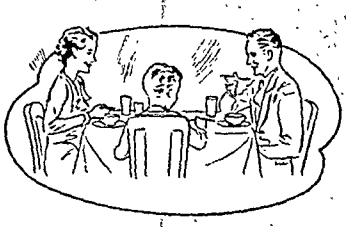


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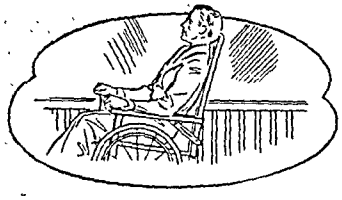
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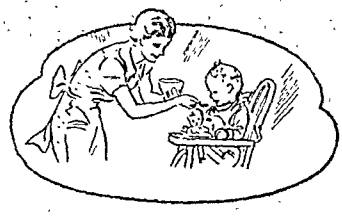


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ported. 520 cases of acute volvulus were recorded. 11.3% were cecal, 18.8% sigmoid and 67.9% small bowel.

Retroposition of the transverse colon is discussed by *Truesdale* who cites the 12th reported case.

Callender and others report an anomaly where jejunal ileal herniation occurred into mesocolon.

Numerous reports of sigmoid volvulus are in foreign articles.

(Also see Dolichocolon).

Callender, C. L., Rusk, G. Y. and Noir, A.: Mechanism, Symptoms, and Treatment of Hernia into the Descending Mesocolon (Left Duodenal Hernia); a Plea for a Change in Nomeclature. *S. G. O.*, 60:1052, June, 1935.
Consiglio, V.: (Clinical Syndrome of Mobile Cecum). *Arch. Ital. di Chir.*, 40:281, May, 1935.
Klinefelter, E. W.: Congenital Absence of the Colon. *Am. J. Dis. Child.*, 50:454, Aug., 1935.
Patel: (Total Atresia of the Large Bowel, Ileosigmoidostomy). *Lyon Chir.*, 32:98, 1935.
Sweet, R. H.: Volvulus of Cecum, Acute and Chronic, with Reports of Eight Cases. *New England J. Med.*, 213:287, Aug. 15, 1935.
Truesdale, P. E.: Retroposition of Transverse Colon; 2 Cases. *J. A. M. A.*, 104:1697, May 11, 1935.

CONSTIPATION

General

The majority of authors on this subject agree with the expression of *Douthwaite* who states "It is sad to reflect that one of the greatest advances in the treatment of gastro-intestinal diseases is being obstructed by the reluctance of the patient to accept simple remedies in the place of unnecessary drugs."

Lancaster in writing about bowel training in the child states "Our experience is that the difficulty is not in getting the mother to do enough for the child, but rather to keep her within bounds and not doing too much."

Alley emphasizes the need for correcting anorectal pathology and gives a thorough rationale for good management.

Murray writes an excellent review covering the etiology and stressing individualized treatment of each case.

Investigative

Frisch experimenting with children, artifically produced constipation in 16 cases allowing bowel movements only once in every 11 days and noticed no immediate harmful results.

Pape in an excellent article reviews the roentgenologic findings in 224 pathological cases showing diagramatically the cycle of disorders of motility as compared to the normal case. The cases are divided into the hypokinetic as opposed to the hyperkinetic, that 62 cases are diarrhetic, 128 constipated, while 34 cases are called occult—that is an abnormally rapid passage combined with normal evacuation. Slightly less than half the cases of constipation showed delayed motility in the proximal colon and an equal number showed normal transport as far as the descending colon, delay beginning with passage of the sigmoid or emptying of the rectum. Only a comparatively few were hyperkinetic type showing abnormally rapid passage throughout the colon.

Physical Therapy and Colonic Irrigations

Physical therapy is recommended in a special rectal tube by *Richter* who believes the escape of gases causes a rapid disappearance of symptoms and that diet, laxatives and massage are useless in advanced conditions where toxins from constipation have affected body organs.

Friedenwald and *Morrison* state that colonic irrigations properly used are of therapeutic value in mucus colitis and intestinal stasis.

Mulinos has written a valuable and instructive article. The various drugs are discussed in detail and their chemical action explained. Laxatives and purgatives are classified as those which depend upon bulk, lubrication or upon the retention of water; those which alter the fluids of the intestine to make them less readily absorbed; and those which stimulate the small or large intestine or both.

Kovacs writes on the physical therapy treatment of constipation in an article following that of Freidenwald and Mulinos in the same journal. These articles in conjunction with each other make the subject matter well rounded. Kovacs, however, does not favor colonic irrigations although he concedes suitable medicated irrigations in colitis may temporarily be employed. Spastic constipation differing from atonic constipation requires nervous relaxation, local sedation, and heat preferably by diathermy.

Dietary and Medicinal

Bastedo writes a valuable and important article reviewing the factors of water, foods and bulk-producing laxatives in the treatment of constipation. Foods act in four ways he states, viz: by distention, mechanical irritation, chemical irritation and by reason of their vitamin content —mainly vitamin B.

Benkert reports an unusual and somewhat humorous case of a huge fecal impaction of masses of fruit seeds, skins, and whole berries.

Bondouy recommends the use of grapes in the treatment of atonic constipation in that they are rich in cellulose, sugar and organic acids.

Brunier states that in colitis with constipation the limitation of carbohydrates and malted products, the avoidance of coarse cellulose, and that the use of enemas for diarrhea are indicated.

Henderson reviews the various purgatives in an excellent well rounded paper and condemns proprietary preparations. States that Ross and Brown reported 28 deaths

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†Jenkinson, E. L.: Cholecystography. J.A.M.A. 107:755 (September 5, 1936)

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REFLEX

Crile states that peptic ulcer, chronic indigestion, and constipation may be termed kinetic diseases and in some cases curable by adrenal denervation or unilateral division of the greater splanchnic nerve.

Trumble considers that abnormal reflex activity may be responsible for certain forms of constipation and advocates sympathectomy in desperate cases to permit the colonic musculature to be released from inhibitory reflexes.

Zuckermann describes a lateral transperitoneal technique for lumbar sympathectomy and ganglionectomy for constipation.

Alley, R. C.: Chronic Constipation: Notes on Etiology and Treatment. *Kentucky M. J.*, 33:590, Dec., 1935.

Bastedo, W. A.: Foods and Bulk Producing Drugs in Treatment of Chronic Constipation. *Rev. Gastro-enterol.*, 2:279, Dec., 1935.

Benkert, G.: (Obstruction of Rectum After Eating Red Currents and Gooseberries). *Deutsche Med. Wchnschr.*, 61:1480, Sept. 13, 1935.

Bondouy, T.: Grapes and Their Therapeutic Properties). *Arch. Med. Chir. de Province*, 25:169, May, 1935.

Brunier: (Chronic Colitis with Stasis and Constipation; Medical Therapy). *Hopital*, 23:423, June, 1935.

Crile, G.: Newer Methods of Treating Peptic Ulcer, Constipation and Indigestion. *New York State J. Med.*, 35:422, 1935.

Friedenwald, J. and Morrison, S.: Value, Indications, Limitations and Technic of Colonic Irrigation. *M. Clin. North America*, 18:1611, May, 1935.

Frisch, I. A.: Constipation in Children: Its Effect on Body Mechanisms. *J. Pediat.*, 6:784, June, 1935.

Kovacs, R.: Physical Therapy in Constipation. *Rev. Gastro-enterol.*, 2:302, Dec., 1935.

Lancaster, F. H.: Constipation and Bowel Training. *South. M. J.*, 28:851, Sept., 1935.

Mulinos, M. G.: Value of Selective Drugs in Treatment of Constipation. *Rev. Gastro-enterol.*, 2:292, Dec., 1935.

Murray, F. H.: Constipation and Its Treatment. *The Medical World*, Sept., 1935.

Pape, R.: Roentgenologic Analysis of Constipation. *Wien. Arch. f. Inn. Med.*, 28:21, Dec. 20, 1935.

Trumble, H. C.: Innervation and Muscular Activities of Distal Colon, with Note on Surgical Treatment (Sympathectomy) of Constipation. *Brit. J. Surg.*, 23:214, July, 1935.

Zuckermann, C.: (Surgical Treatment of Constipation and Painful Colon). *Rev. Mexicana de Cirug., Ginec. y Cancer*, 3:393, July, 1935.

DIVERTICULOSIS AND DIVERTICULITIS

By far the most outstanding publication on this subject is that of *Lunding* who has written a monograph on the subject. The literature is a review quite complete and there is a discussion of every phase of diverticulum formation. The author bases his report on 103 cases. The cases were from 1921 to 1934. In routine colon cases X-rayed, diverticulum were present in 3.2-4.5% of cases. Males were 46.6% and females 54.4%. They were more common from 40-60 years of age. 68.9% were located in the sigmoid exclusively whereas 90.3% showed sigmoid involvement, 99% of the cases showed diverticula present either in the descending colon or sigmoid or both. 55% of cases showed inflammatory changes present as demonstrated by X-ray.

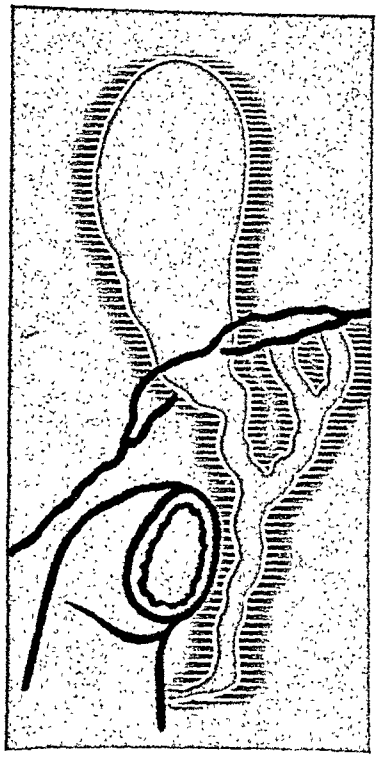
The author is of the opinion that the catalase test of fecal matter is of importance in the diagnosis and prognosis of the condition and found it increased over the normal amount in 60 pathological cases using as normal controls 93 tests from 42 normal cases. The method of Norgaard was used. The catalase is supposed to be an iron porphoryn protein compound which acts as a hydrolytic agent.

Abell studying all forms of diverticula states 5% of subjects over 40 years of age have diverticula of the colon.

Clairmont points out the dangers of diverticulosis and warns against nimless surgery.

Cone in an important paper cites a b. coli bacilluria in 3 cases of diverticulitis which he believes occurred by reason of mucosal permeability, resultant bacillemia and consequent bacilluria.

Friedenwald and *Feldman* report 50 cases ranging in



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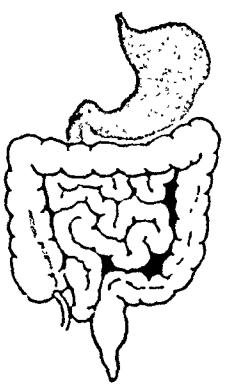
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**Arch. Int. Med 38 647,1926 Am. J. Surg 7:455,1929.
***Ann. Int. Med 6:1463 1933 J. Lab & Clin. Med 19:567, 1934

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age from 34 to 79 years of age. The paper is excellently done. The authors found 8-10% of patients affected by gastro-intestinal disturbances had diverticuli, is twice as common to males as females and usually occurs after 40 years of age. Their cases also showed that it is usually multiple, occurs most frequently in the sigmoid, then in frequency of occurrence in the sigmoid, descending colon, transverse colon, ascending colon and appendix. Roentgen-ray examination showed irritable colon in 32 cases, duodenal ulcer in 2, cholecystitis in 3, adhesions in 25 and diverticula elsewhere in the gastro-intestinal tract in 4 cases. 38 cases were treated medically and 8 surgically. The authors among various methods of their outlined treatment recommend filling the diverticula with a barium bismuth mixture.

Manning reviews the subject and sanely advocates surgery for only the complicated cases and advises when surgery is resorted to, to avoid the area effected if possible.

Moynagh reports on 25 cases at St. Bartholin's Hospital in a series of papers. 16 were colon, 1 cecum, 4 duodenum, 1 stomach, 2 oesophagus, and 2 pharynx. Moynagh classifies diverticulitis as belonging to those with symptoms of obstruction, urinary symptoms or with pelvic symptoms when of the female group. They occur where conditions of stress are produced, are probably congenital and partly on a neurological basis due to a disruption of the autonomic nervous system.

Ochsner and *Bargen* state that 7% of 2,747 patients examined roentgenologically at the Mayo Clinic showed diverticulosis which being 0.4% of clinic patients is probably too low inasmuch as 6.9% were found in 447 necropsies during the same period. Males exceeded females 1.25 to 1 but diverticulitis showed 2.75 to 1. 11% showed diverticulitis and 13% gave a suggestive history of previous trouble. Constipation was present in 40% but in uncomplicated diverticulitis of the sigmoid was present in 58%. 6% of the diverticula showed malignancy.

Pessagno reports a rare case of simple diverticulitis of the cecum.

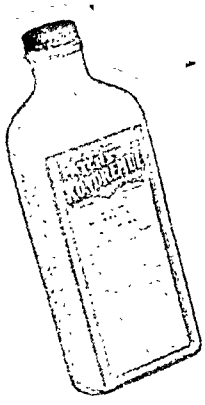
Underwood reports an analysis of 157 cases of diverticulosis as diagnosed roentgenologically at the Cleveland Clinic. 68.9% occurred in patients between 50 and 69, and sex was equally divided. 104 were sigmoid, 27 descending colon, 13 transverse colon, 6 ascending colon, 6 generallized colon, and 2 cecum. 39 cases were associated with diverticulitis or an incidence of 25%; 2 cases had an associated malignancy of the colon.

Rutledge reports a study of 70 cases of diverticulosis in which most of the cases were past 40 years of age and were victims of chronic constipation. One of the cases was a boy 17 years of age.

Abell, I.: The Diagnosis and Treatment of Diverticulitis and Diverticulosis. *S. G. O.*, 60:370, Feb., 1935.
Chairmont, P.: (Diverticulosis of the Large Intestine). *Chirurg.*, 7:270, May 1, 1935.
Cone, R. E.: Sigmoid Diverticulitis and Urinary Tract Infection: Case Reports. *South. M. J.*, 28:535, June, 1935.
Friedenwald, J. and Feldman, M.: Diverticulosis and Diverticulitis. *Rec. Gastro-enterol.*, 2:97, June, 1935.
Lunding, Karl: The Symptomatology of Diverticulum Formations of the Colon. *Acta Medica Scandinavica*, Supplement 72, 1935.
Manning, V. R.: Diverticulosis and Diverticulitis. *The Medical World*, 53, June, 1935.
Moynagh, D. W.: Diverticula of Colon. *St. Barth. Hosp. J.*, 42:101, July; 208, Aug.; 223, Sept., 1935.
Ochsner, H. C. and Bargen, J. A.: Diverticulosis of the Large Intestine; An Evaluation of Historical and Personal Observations. *Ann. Int. Med.*, 9:282, Sept., 1935.
Pessagno, D. J.: Diverticulitis of Cecum. *Bull. School Med. Univ. Maryland*, 20:39, Oct., 1935.
Rutledge, C. P.: Diagnosis of Diverticulitis and Diverticulosis of the Colon, with Special Reference to the Roentgen Study of These Conditions. *South. M. J.*, 28:303, 1935.
Underwood, C. C.: Diverticulosis and Diverticulitis of Colon. *Kansas M. Soc. J.*, 36:488, Dec., 1935.

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"... we know that in the infant and growing child alkali in excess of acid must be stored."

Growth and Development of the Child, Part III, White House Conference on Child Health and Protection, New York, 1932, p. 213.

BUT—

many diets are acid-forming

AS pointed out in the Journal of the American Medical Association (Queries and Minor Notes, 103:701, 1934), "... most high carbohydrate foods of the artificial and refined types are lacking in the basic elements. These basic ions, such as sodium, potassium, and calcium, are necessary for the neutralization and excretion of the various acid waste products of the body. Hence carbohydrates may be implicated in the occurrence of such an acid state by displacing other necessary food products from the dietary."

Ordinary cereals and cereal products, meat, and eggs—all produce an acid ash when burned in the body, yet they form the mainstay of the average diet. Although this preponderance of acid-forming foods is not definitely known to have great significance for the health of normal adults, a number of authorities advocate a basic or alkali-forming diet for children and pregnant women.

INFANCY AND CHILDHOOD. "Alkaline diets are essential for infancy where growth is rapid," declares Shohl. He calculates the need as 10 c.c. excess of 0.1 normal base per kilo day.[1] Babies fed on breast milk stored an excess of base over acid, the range being from 31 to 56 c.c. 0.1 N base per day, is the finding of the Committee on Growth and Development of the White House Conference on Child Health.[2] Lippard and Marples observed greater increases in weight of infants receiving basic diets as compared with controls on acid-forming feedings.[3]

PREGNANCY AND LACTATION. Shohl states, "Pregnancy and lactation require additional alkali—a minimum of 150 c.c. of 0.1 N base per day."[1] Coons and associates, from acid-base balances taken upon normal pregnant women receiving basic diets, determined that the storage of basic substances was even greater than estimated by Shohl. "This may be some indication," they say, "of the magnitude of the maternal needs exclusive of fetus."[4]

As the chief alkali-forming foods are fruits, vegetables, and milk, the ordinary basic diet consisting of these foods is likely to be low in calories and often does not appease hunger. But Pablum—the only base-forming cereal*—offers a way to add muffins, cereal, puddings and similar "filling" foods to the usual basic diet. Pablum, moreover, is richer than ordinary cereals in calcium, phosphorus, iron, and copper and supplies vitamins B and G.

[1-4] *Bibliography on request.* *Mead's Cereal (Pablum in uncooked form) is also base-forming.

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Pablum (Mead's Cereal thoroughly precooked) is a palatable basic cereal consisting of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa leaf, beef bone, brewers' yeast, iron salt and sodium chloride.



Cereal	Base	Acid
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Farina		11.0
Oatmeal		12.9
Wheat, whole		11.5
Cornmeal		5.3
Barley		10.1
Rice		8.1

Figures given in the above table are based on 100 grams of food and represent cubic centimeters of normal acid or base.

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A Study of the Glycemic Response in Patients With Biliary Tract Disease*

By

HENRY A. RAFSKY, M.D., F.A.C.P.†

NEW YORK, NEW YORK

BILIARY tract disease is undoubtedly, more common in diabetics than non-diabetics. This fact has been stressed by Warren (1), Joslin (2), Boyd (3) and many others. While it is generally recognized, that these two diseases are frequently associated, a difference of opinion still exists as to the etiological rôle which gall tract disease plays in diabetes mellitus. Duncan (4) regards the former as a frequent forerunner of diabetes. Mosenthal (5) has pointed out, that the management of gall stones and their complications, with a view to effective prevention of damage to the carbohydrate tolerance has received scant attention. Joslin (2) again, in his most recent work on this subject, stated that we can no longer assign to gall bladder disease a primary causative role in diabetes. Boyd (3) expressed the view that gall stones are more likely the result of the metabolic disturbance rather than, in any sense, a cause of the disease.

The underlying cause of the disturbed carbohydrate metabolism and the explanation for the marked and lasting improvement in the diabetes, which sometimes follows gall stone operations, are also debatable points, resulting from the frequent association of biliary tract disease and diabetes. Jordan (6) regards this improvement in the sugar tolerance, in the same category, as that observed, following the treatment of any active infection, such as a carbuncle. Rabinowitch and Bazin (7) reported some cases of cholelithiasis, with hyperglycemia, in which decreased blood sugar levels, were observed, after operation. They thought that chronic pancreatitis was the cause of the decreased glucose tolerance and that, in these cases, exploration of the common duct, in addition to cholecystectomy, was advisable. Lande and Pollock (8) again, cited their cases of biliary tract disease, with hyperglycemia as well as the case reports of other observers, in which improvement in the diabetes followed gall tract operations, to show that there was a correlation between the disturbance of the carbohydrate metabolism and the degree of impairment of hepatic function. Jacobi (9) also cited his cases, to emphasize the relation of liver damage to hyperglycemia, in obstructive jaundice, due, amongst other affections, to gall stone diseases.

In view of the above, it was deemed of interest to study the glycemic response, in a series of non-diabetic patients, with and without biliary tract disease. The incidence of hyperglycemia was noted in these patients, as well as the effect of surgical and non-surgical measures upon the carbohydrate tolerance. These blood sugar findings were then compared with those observed in the patients comprising the control group.

A series of one hundred and nine patients, ranging in age from twenty-one to fifty-seven years, was studied. The duration of their symptoms varied from eight months to fifteen years. The patients were grouped as follows:

1. Fifty-nine patients with gall stone disease.
2. Fifty patients with abdominal symptoms due to affections other than biliary tract disease. These patients comprised the control group.

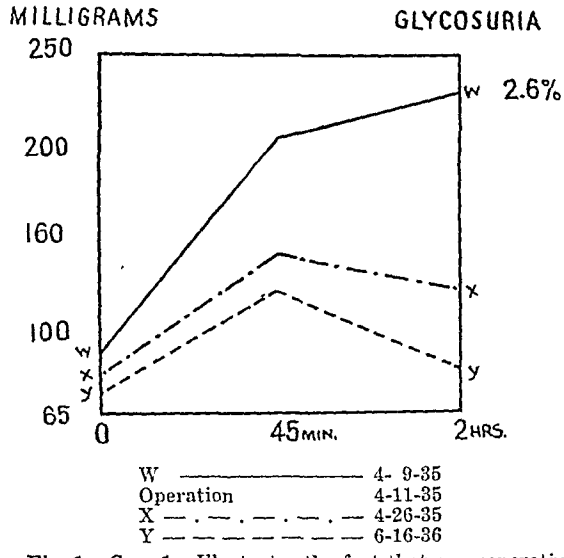


Fig. 1. Case 1. Illustrates the fact that a preoperative hyperglycemic response was followed, after cholecystectomy, by a restoration of the normal glucose tolerance. Mrs. M. S., 39 years old, white, married, complained of attacks of abdominal pain for five years. Operation 4-11-35: Cholecystectomy for calculous cholecystitis; right lobe of liver involved in an extensive fibrosis; left lobe normal.

METHOD OF PROCEDURE

Specimens of blood were obtained for the glucose tolerance test, while the patient was fasting, at forty-five minutes and two hours after the ingestion of one hundred grams of glucose. The determination of the blood sugar was carried out, according to the Benedict Copper Method (10), which places the normal fasting blood sugar between 65 to 100 milligrams in one hundred cubic centimeters of blood. In the patients, who were subjected to operation, the glucose tolerance test was performed prior to and at periodic intervals after surgical intervention. The ingestion of carbohydrates was not restricted before the operation, irrespective of the blood sugar levels. After the operation, the usual post-operative diets were given.

*Read at the New York Academy of Medicine before a Combined Meeting of the Section of Medicine and the New York Gastro-Enterological Society, November 17, 1936.

From the Einhorn Clinic, Medical and Surgical Divisions of the Lenox Hill Hospital, and [illegible] Surgical Divisions of the Beth Israel [illegible]

†Attending Gastro-Ente [illegible] Associate Gastro-Enterologist, Lenox Hill Hospital.

Submitted January 12, 1937.

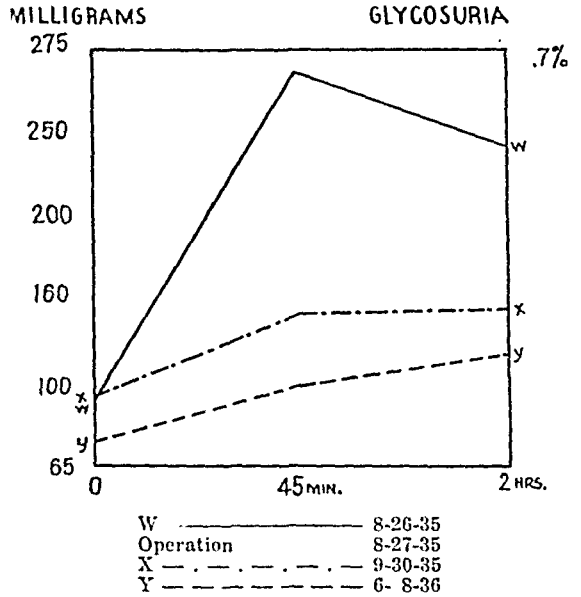


Fig. 2. Case 2. Illustrates the fact that a preoperative hyperglycemic curve was followed, after operation, by normal blood sugar levels, but the curves were not of a normal type. Mr. L. S., 46 years old, gave a history of biliary tract disease of ten years duration. Operation 8-27-35: Cholecystectomy for calculous cholecystitis. The cystic duct was rather long and extended almost to the Ampulla of Vater. The liver was the seat of a fibrosis around the gall bladder bed.

In order to eliminate, in so far as it was possible, the systemic role of infection, the blood for the glucose tolerance test was obtained, while the temperature, blood count and sedimentation rate were within normal limits. Patients with malignancy, jaundice or hyperthyroidism were excluded from this investigation, because hyperglycemia is often encountered in these diseases.

TYPES OF BLOOD SUGAR CURVES OBSERVED

The types of blood sugar curves which were observed during the course of this study were as follows:

A. A normal blood sugar curve.

B. A curve with a normal fasting blood sugar, a continued upward trend beyond 160 milligrams reaching the peak at forty-five minutes and then a return to a normal or almost normal blood sugar level at the end of two hours.

C. A flat curve which was characterized by a normal fasting blood sugar level and with little or no fluctuation, until the end of two hours. This type of curve is often seen in endocrine dysfunction.

D. A curve with a normal fasting blood sugar level, a gradual rise beyond 160 milligrams reaching the peak at the end of forty-five minutes and then a slight descent to the end of two hours.

E. A curve with a normal fasting blood sugar level, a continued upward trend beyond 160 milligrams, reaching the peak at forty-five minutes and then a flat curve from this point on, until the end of two hours.

F. A curve with a normal fasting blood sugar level, then a gradual rise beyond 160 milligrams, with the peak being reached at the end of two hours.

A blood sugar curve of the type B, D, E and F, was regarded as a hyperglycemic response. The average fasting blood sugar level observed in this study was 81 milligrams in 100 cubic centimeters of blood, the lowest being 64 and the highest 97 milligrams. The highest blood sugar level reached after the ingestion of the glucose was 273 milligrams in 100 cubic centimeters of blood.

CLINICAL STUDY

Group 1. This group comprised fifty-nine patients with gall stone disease, ten of whom were males and forty-nine females. In fifty-two of the patients who were operated upon, the glucose tolerance test, preoperatively, revealed the following: A hyperglycemic response in thirty-two patients (61.5%); a normal blood sugar curve in seventeen (32.7%) and a flat curve in three patients (5.8%).

Of the thirty-two patients with evidence of a decreased glucose tolerance, the preoperative glycemic response showed the following: A type "B" curve in eight patients (25.0%); a type "D" curve in eleven patients (34.4%); a type "E" curve in six patients (18.8%); a type "F" curve in seven patients (21.8%).

In twenty-five of the thirty-two patients with a preoperative hyperglycemic response, a definite improvement resulted in the glucose tolerance after the operation, regardless of whether cholecystectomy alone, or cholecystectomy together with choledochotomy were performed. This improvement was observed from two weeks to six months or more after the operation. In five patients the sugar tolerance test did not show any material change after operation. The postopera-

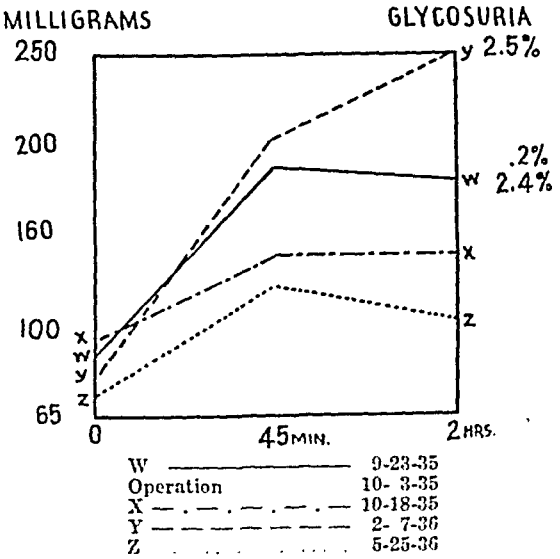


Fig. 3. Case 3. Illustrates the fact that a preoperative hyperglycemic response was followed, after operation, by a reduction in the blood sugar levels, although the curve was not a normal one. Several months later, further evidence of a decreased tolerance was observed. The patient, who was five feet tall, weighed 70 kilograms. She was placed on a diet composed of carbohydrate 185 grams, protein 85 grams and fat 50 grams. An improvement in the glucose tolerance was then observed, both in the blood sugar levels and type of curve. Mrs. P. D., 55 years old, white, married, gave a history of attacks of biliary colic on and off for ten years. Operation 10-7-36: Cholecystectomy for calculous cholecystitis. The common duct, which was dilated, was explored but no stones were found. The liver was enlarged.

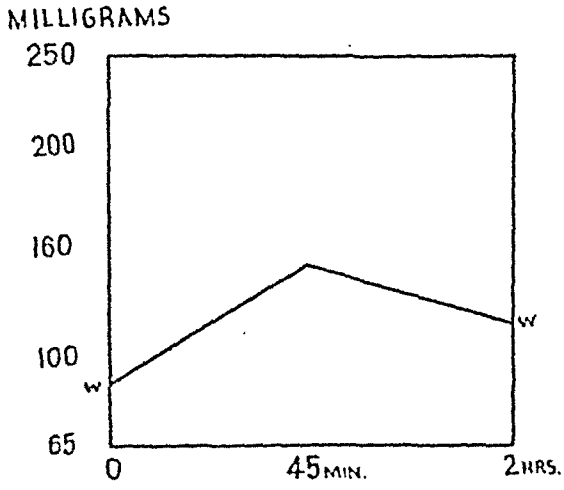


Fig. 4. Case 4. Illustrates the fact that a comparatively normal blood sugar curve may be present in a patient, with gall stone disease with marked pancreatic involvement. Mrs. S. B., 33 years old, white, married, gave a history of attacks of pain in upper right quadrant, on and off, for six years. Operation 5-7-35: Cholecystectomy was performed for calculous cholecystitis. The fat of the falsiform ligament as well as omentum and all retroperitoneal tissues were studded with fat necrosis as a result of an acute pancreatitis. Palpation of pancreas showed it to be thickened, hardened and swollen. Numerous stones were present in the gall bladder. The liver was large and soft.

tive improvement, which was noted in the twenty-five patients was as follows: In fourteen patients there was a complete restoration of the normal carbohydrate tolerance. In four patients the blood sugar levels were within normal limits but the curves were not of a normal type. Two of these four patients, who were over weight, subsequently showed further evidence of a decreased glucose tolerance. They were placed on a high carbohydrate low fat diet, which Rabinowitch (11) has termed a "high carbohydrate, low caloric diet." Following this regime an improvement was noted in both the blood sugar levels and the type of curve. In four patients the curves had a more normal trend but the blood sugar levels, although lower, were not within normal limits. In three patients there was a postoperative restoration of the normal tolerance within three months but after a return of the abdominal symptoms, a hyperglycemic response was again observed. After the patients became symptom-free, normal blood sugar curves were found.

In two patients who returned, after cholecystectomy, complaining of diarrhea, loss of weight and weakness, a flat blood sugar curve was observed. As this type of blood sugar curve is often encountered in hypothyroidism, hypopituitarism, hypoadrenalism and ovarian dysfunction, it was deemed advisable to treat these patients on an endocrine basis. Following this plan of therapy a clinical improvement and normal blood sugar curves were noted.

A blood cholesterol was determined in twenty-one of the thirty patients with a preoperative hyperglycemic response. The average blood cholesterol reading was 197 milligrams in 100 cubic centimeters of blood.

Group 2. The control group comprised fifty patients who were suffering from affections such as inguinal hernia, chronic appendicitis, nephrolithiasis, peptic ulcer, constipation and fibroid of the uterus. Fourteen of the patients were males and thirty-six were females.

A normal blood sugar was found in thirty-nine patients (78.0%) of the control group. In the remaining eleven patients (22.0%) a hyperglycemic response occurred. A type "E" curve was observed in one of these patients and a type "B" curve was found in ten patients. Amongst the eleven patients in the control group to give a hyperglycemic response were eight, suffering from peptic ulcer. Altogether fifteen patients with peptic ulcer were studied.

At times it was observed, in both the gall stone patients as well as those in the control group, that the glucose tolerance test immediately after operation showed an increased blood sugar curve as compared to the glycemic response present before operation. This postoperative decreased glucose tolerance, could be accounted for on the basis of an intercurrent infection such as a broncho-pneumonia or surgical reaction. Within a period of three months, the glucose tolerance test, in these patients, again showed normal blood sugar curves.

The following case reports will illustrate the varied clinical phenomena which were observed during the course of this study.

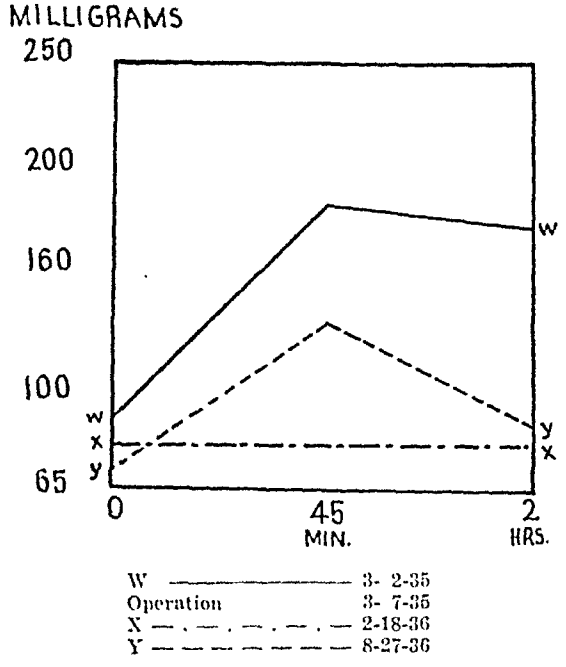


Fig. 5. Case 5. Illustrates the flat type of blood sugar curve in a patient, who complained of nervous and abdominal symptoms without severe pain, after cholecystectomy. Mrs. H. G., 41 years old, white, married, had a cholecystectomy performed for a calculous cholecystitis. She returned about one year later complaining of epigastric distress, a choking sensation, diarrhea, insomnia and a loss of fifteen pounds in weight. The patient was treated on the basis of an ovarian dysfunction. Lutein was administered parentally three times a week. About six months later a normal blood sugar curve was found; the patient had gained ten pounds and was comparatively symptom free.

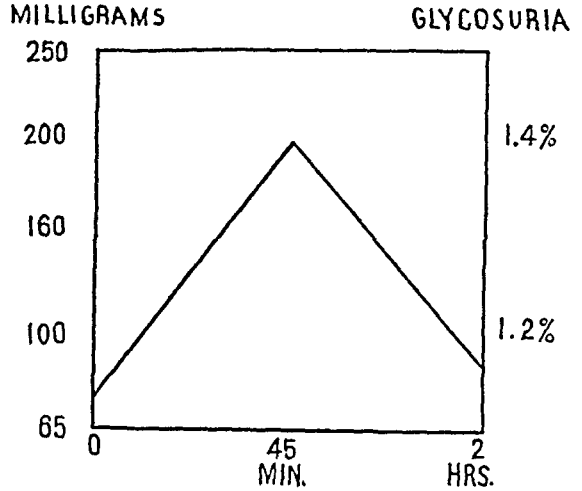


Fig. 6. Case 6. Illustrates the type of curve seen in patients with peptic ulcer and a hyperglycemic response. Mr. H. S., gave a history of duodenal ulcer of eight years duration.

DISCUSSION

A comparative study of the blood sugar levels was made in patients with and without biliary tract disease. It was found that a hyperglycemic response was present in 61.5% of the fifty-two patients with gall stone disease, who came to operation and in only eleven (22.0%) of the fifty patients in the control group. Surgical intervention resulted in an improvement of the carbohydrate tolerance in most of the patients in Group 1, although an improved glucose tolerance, after operation, did not always signify a normal type of curve. In two of the cholecystectomized patients a high carbohydrate low fat diet was employed to influence the blood sugar index and the type of curve. This was illustrated in Case 3. In two patients with nervous and abdominal symptoms and a flat blood sugar curve, after cholecystectomy, an attempt was made, as was illustrated in Case 5, to influence the clinical course and the glycemic response by the use of endocrine therapy.

The types of curves observed in Groups 1 and 2 have been outlined. In this connection it is interesting to note that in all of the ulcer patients with a hyperglycemic response, a type "B" curve was observed. Although penetration into the pancreas is not an infrequent complication of peptic ulcer, still, the association of peptic ulcer and diabetes is comparatively uncommon. Jordan (12) found one case of glycosuria and high blood sugar curves present in 351 cases of peptic ulcer. Eustermann and Balfour (13) also stressed the rare occurrence of glycosuria in gastric and duodenal ulcers. Therefore a hyperglycemic response with a type "B" curve cannot be regarded as definitely pathological in its relation to a disturbed carbohydrate metabolism, as the other types of curves which were found in most of the patients in Group 1.

Various explanations may be advanced, to account for the decreased glucose tolerance in many of the gall stone patients in Group 1, and for the improvement in the glycemic response found in most of the patients, after surgical intervention. To attribute these phenomena, solely to the mere presence and treatment of an active infection, somewhere in the body, is unsatisfactory. For, in this study, an attempt was made, in so far as it was possible, to rule out the systemic rôle of infection. Until recently, pancreatic dysfunction was regarded as fundamentally important in causing a disturbed carbohydrate metabolism. But, as a result of the work of Mann and Magath (14), Soskin and his co-workers (15, 16), it appears that the liver is the probable determinating factor in regulating the blood sugar levels, after the ingestion of glucose. Mattina (17) observed, that in dogs, hyperglycemia was a constant finding in experimental stenosis and occlusion of the common bile duct. He stated that the increase in the blood sugar index, both in height and rapidity of development, varied according to the diversity of the liver changes, which were produced in these cases. Canterow (18) has emphasized the fact that hepatic functional impairment is frequently found in apparently uncomplicated gall bladder disease.

The varied clinical phenomena, observed in this study, some of which were illustrated in the case reports, would tend to point to hepatic rather than pancreatic involvement, as the underlying cause of the disturbed carbohydrate metabolism. It is also reasonable to assume that the postoperative improvement in the glucose tolerance, which was noted in most of the gall stone patients, was due to improved liver function. But it must also be admitted that in long standing biliary tract disease, the pancreatic rôle as a cause of the increased blood sugar levels, cannot be entirely eliminated, as, under these circumstances, degeneration of the islets of Langerhans may eventually take place.

SUMMARY

A decreased glucose tolerance was observed more frequently in non-diabetic patients, with gall stone disease, than in those without this affection.

The type of curve observed in most of the patients with a hyperglycemic response, in the control group, was different from that found in the majority of the patients with cholelithiasis.

Surgical intervention, resulted in an improvement in the glucose tolerance, in most of the gall stone patients.

The varied clinical phenomena observed, pointed to a hepatic dysfunction, rather than a pancreatic impairment, as the probable underlying factor in the disturbed carbohydrate metabolism.

CONCLUSIONS

1. Cholelithiasis, in non-diabetic patients, is a comparatively frequent cause of a disturbed carbohydrate metabolism.

2. The early removal of the gall stones will probably lessen the incidence of diabetes mellitus in these patients.

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Studies on the Neutralization Test of Gastric Acidity in Relation to General Disease*

By

KENNETH PHILLIPS, M.S., M.D.

MIAMI, FLORIDA

THE value of analysis of gastric contents in the study of ulcer has long been considered of great significance. More recently attention has been turned, especially among clinicians, to its value in the pathogenesis, diagnosis and treatment of other gastro-intestinal syndromes as well as disease in general. The result of this expansion in thought has been the appearance of periodical reports such as those of Haden (1), Apperly (2), Murry (3) and others dealing with the relationship between a gastric factor and certain types of blood dyscrasias and Christie's (4) suggestion of the etiological relationship between achlorhydria and many of the deficiency syndromes. Clinical study of the gastric secretory function, in spite of the vast amount of investigation, has proven to be, to a great extent, variable and disappointing. The various reasons for this are well understood and have been extensively discussed.

The experimental work of Mirai, Boldyreff (5), MacLean and Griffiths (6), Mathews and Dragstedt (7) and many other investigators showing the definite ability of the contents of the normal stomach to neutralize hydrochloric acid when introduced in physiological concentration (0.5 per cent) has been observed with keen interest. Within the past two years Elman and McLeod (8) and Levy (9) have, undoubtedly, established the clinical application of the above experimental work to ulcer. They have properly given to this clinical application a name "the neutralization functional test of the stomach." The physiological basis for this function of the gastric contents, together with the possible clinical value, including the details of technique, are discussed so thoroughly and extensively in both reports that they need not be reiterated here. Both reports are most convincing, both limited, however, to the study of the neutralization test in relation to peptic ulcer, Levy reporting in addition its application to pylorospasm and chronic appendicitis. The call for more extensive work and broader application of the test so frankly emphasized by these investigators is self evident.

This study and report is an attempt further to confirm the work reported by these observers and in addition to modify their technique, if possible, in order that it becomes more practicable from a standpoint of simplicity especially to the individual clinician not in possession of an associated laboratory equipment whereby it is distinctly to his, as well as his patient's, advantage to be able to complete both the secretory and neutralization studies at one sitting. Since the clinical reports of Elman and McLeod and Levy are so convincing in relation to peptic ulcer, pyloric obstruction and possibly chronic appendicitis, it becomes self evident that we should attempt to determine whether or not its clinical value is limited to these conditions alone or if the test also possesses value not only in other diseases of the gastro-intestinal tract but in some diseases not primarily associated with the tract such as those of allergic nature.

MODIFICATION OF TECHNIQUE

The technique described by Elman, McLeod and Levy consists of passing a small duodenal tube, the same as for the fractional gastric analysis, emptying the stomach by aspiration then instilling 300 c.c. of 0.5% (Elman) or 0.6% (Levy) HCl into the stomach; aspirating small specimens at ten to twenty minute intervals for seventy to one hundred twenty minutes; titrating with tenth normal sodium hydroxide and plotting a fractional curve. These tests were made separately from their comparative secretory fractional Ewald meal determinations on the same patients.

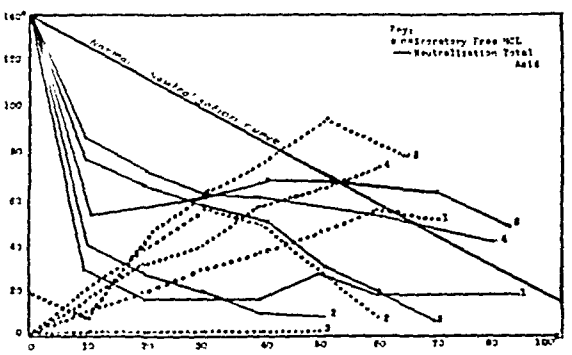
The modification offered here is concerned with further simplifying the technique which renders its application to the individual clinician more feasible. In the first place it is well recognized that mechanical distention of the stomach from any fluid may act as a stimulus. Therefore, if the total volume used can be reduced, the results are likely to be more accurate. This can be accomplished by shortening the time intervals of aspiration to ten minutes and the fractional volumes to 10 c.c. each. It is then necessary to use only one hundred fifty to two hundred c.c. of the 0.5% HCl. A second aggravating factor to the accuracy of the test is also eliminated by this reduction in volume

*From the Department of Medicine: James M. Jackson Memorial and Victoria Hospitals.

Submitted October 8, 1936.

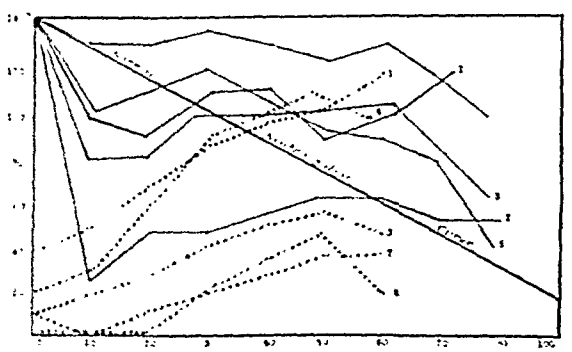
namely, the nervousness from distention even with vomiting which has been so common in our experience with the larger volumes.

It is, of course, obvious that fractional secretory curves are desirable for comparison in all cases. It has, undoubtedly, been established that a secretory test meal consisting of seven per cent alcohol is equally accurate, if not more so, than the Ewald meal. Since this is a liquid meal it is possible to theoretically, at least, empty the stomach after the secretory curve has been obtained. Then, if the subsequent introduction of the 0.5 HCl will produce curves which conform to those established by Elman and Levy, we now have a technique whereby both curves can be obtained at a single intubation. Furthermore we also now obtain both curves under the same physiological and psychological conditions both of which can easily change from time to time and both of which, undoubtedly, affect the accuracy of the tests when performed separately. Reference to Figure 1, Graph I and II reveals that these modifications can be accomplished with sufficient clinical accuracy in both normal and ulcer patients. While there is apparently a slight lagging in the beginning of the neutralizing curve for possibly the first ten minutes it then assumes a course similar to that established by Elman and Levy. This slight inaccuracy is soon overcome by experience in



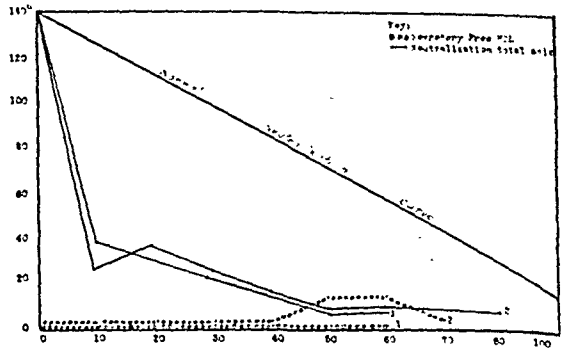
Time in minutes

Fig. 1. Graph I. Secretory and neutralization curves in five normal cases. Note normal variation in neutralizing power, independent of secretory curves.



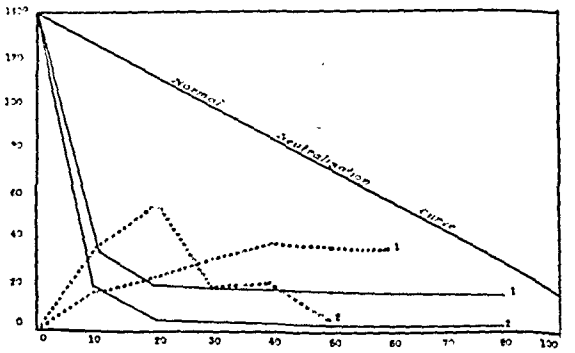
Time in minutes

Fig. 1. Graph II. Secretory and neutralization curves in five cases of Peptic Ulcer. Note delay in curves as compared to normal neutralizing curves in Graph I.



Time in minutes

Fig. 2. Graph I. Secretory and neutralization curves in two cases of peptic ulcer with achlorhydria. Note difference between neutralizing curves and those of Fig. 1, Graph II.



Time in minutes

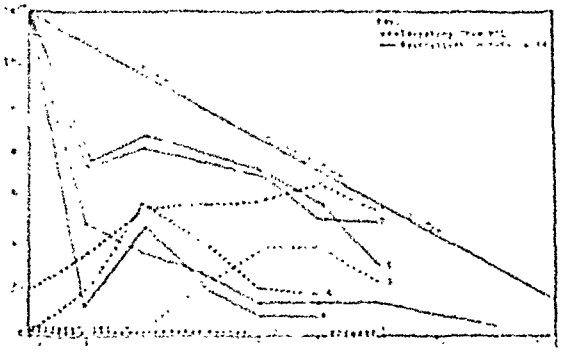
Fig. 2. Graph II. Secretory and neutralization curves in two cases of Gastric carcinoma (proven at autopsy). Note increased neutralizing power in presence of normal free HCl.

one's individual interpretations which have to be developed gradually in either case.

METHOD OF STUDY AND RESULTS

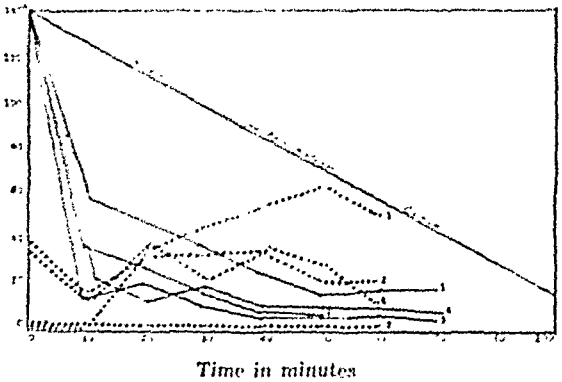
Five normal healthy individuals (volunteers) and five cases with duodenal ulcer confirmed clinically and by X-ray findings were selected and exposed to fractional gastric secretory analysis using seven per cent alcohol as the test meal. At the completion of the secretory test the stomach was emptied and one hundred fifty to two hundred c.c. of 0.5% HCl immediately instilled and the aspirations continued at ten minute intervals. It will be noted upon reference to Figure 1 that both groups present graphic curves which conform closely in general type to those established by Elman and Levy. Two important facts, however, must be kept in mind. The gastric power to neutralize in normal individuals is quite variable except that in our experience we have never found it to be delayed above the normal curve line established by Elman. In many cases, however, it is markedly increased, the curve assuming a sharp drop even to the zero or base line. We studied the curves in over thirty cases in order to be certain that this variation is correct. The second fact which has come to our observation is in the ulcer case (confirmed by clinical and X-ray studies) with an associated absence of free hydrochloric acid during the secretory meal. The

neutralizing curves in these cases assume a sharp downward course and fail to reveal the usual delay shown in the other ulcer cases. Two such curves are shown in the graphs of Elman and McLeod (7) but they were in cases following gastric resection and, therefore, do not cast helpful light upon the explanation. In this series we were unusually fortunate in being able to study two cases, (1) and (2) illustrated in Figure 2, Graph I. Case (1) possessed a large duodenal ulcer involving the major portion of the cap while case (2) presented the most extensive ulceration of the gastric lesser curvature we have ever observed. Curious enough the emptying time of the stomach in both cases was much more rapid than normal, therefore, it is safe to assume that no pyloric obstruction was present in either case. Just at the time we were studying these two cases a fortunate coincidence occurred in that there appeared two cases of carcinoma, one primary in the stomach with a palpable mass, the other metastatic, secondary to a breast malignancy (both were confirmed at autopsy). Both were extensive in invasion and were producing pyloric obstruction with retention and vomiting in one case. Studies of the secretory and neutralizing curves as compared to the achlorhydria ulcer curves are most interesting since it will be seen (Figure 2, Graph II) that the secretory functional curves are at the upper normal level while the neutralizing curves assume a sharp drop almost identical with the ulcer curves in Graph I.



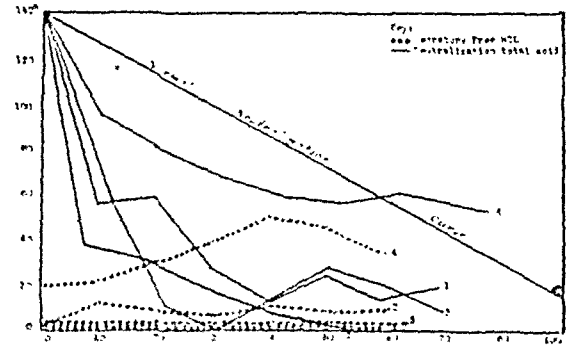
Time in minutes

Fig. 3. Graph I. Secretory and neutralization curves in four cases of vague gastro-intestinal symptoms. No organic findings except spastic colon.



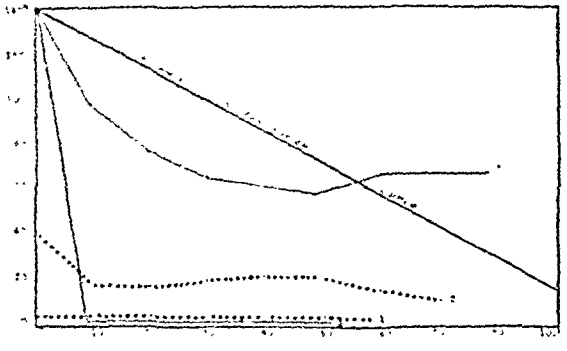
Time in minutes

Fig. 3. Graph II. Secretory and neutralization curves in four cases of liver and gall bladder disease. Note increased neutralizing power independent of secretory curves.



Time in minutes

Fig. 4. Graph I. Secretory and neutralization curves in four cases of allergic disease. All within normal with the exception of Case 4.



Time in minutes

Fig. 4. Graph II. Secretory and neutralization curves of Pellagra (Case 1) and chronic appendicitis with ovarian cyst (Case 2). Note marked increase in neutralizing power in Case 1; delayed in Case 2.

This observation, I feel, is very important from the standpoint of analysis and interpretation. I suppose it is correct that one should never venture an opinion without unquestionable basic facts; but after three years of experience and study in these curves in every case who has been exposed to gastric analysis, I am more and more of the opinion that there is some mechanism entering into this neutralizing function other than the regurgitation of duodenal contents into the stomach. In the two ulcer cases the pyloric opening was probably even more relaxed than in the normal because the emptying time was so rapid. Regurgitation, therefore, of duodenal contents could be more accessible which might contribute to both achlorhydria and increased neutralizing power. However, in the carcinoma cases there was marked pyloric obstruction and while they manifested notably high secretory curves for malignancies, the neutralizing curves assumed the almost identical course of the ulcers. There is only one factor which these cases share in common, that of extensive pathological involvement. In one of the ulcer cases almost half of the entire distal end of the lesser curvature was involved, in the other nearly two-thirds of the cap. In both of the malignancies the involvement was extensive. Why the increase in neutralizing power in the presence of pyloric obstruction whereby the regurgitation of duodenal juices is re-

duced? Is it not suggestive that the stomach itself might possess some neutralizing function which might be inhibited under some conditions, stimulated under others?

GASTRO-COLONIC SYNDROME GROUP

An attempt is made to classify, as a group, eighteen cases of this type so familiar to every internist. The complaint is a vague indifferent form of sub-acute or chronic indigestion with gaseous distention often hinging upon some foreign foci of irritation or infection in the upper respiratory or genito-urinary tracts. These cases are usually organically negative throughout the gastro-intestinal pathway except for spasm of the colon and very often associated pyloro-spasm under the barium meal. The eighteen cases fell into the following groups: Chronic spastic colon with mucus, three; spastic colon without mucus, five; psychoneurosis, two; chronic follicular tonsillitis, four; chronic bronchiectasis, one; genito-urinary pathology, three. Studies of the secretory and neutralizing curves (Figure 3, Graph I) reveal them to be so variable and inconstant as to be entirely unreliable. However, those variations are within what would be obtained in any normal series of patients. They do demonstrate, however, the remarkable constancy of the power of gastric contents to neutralize free hydrochloric acid and also that this neutralizing curve assumes its own course independent of the secretory curve. These facts are clearly demonstrated in cases one and two of the graph. The neutralization functional test then in cases of chronic gastro-colonic indigestion are apparently of no value as a diagnostic aid.

LIVER AND GALL BLADDER DISEASE

Eight cases of liver and gall bladder disease all confirmed at subsequent operation or autopsy were exposed to both secretory and neutralization tests. Gall stones were present in three, hepatitis and gall bladder disease without stones in four and hypertrophic cirrhosis in one. All cases manifested an associated indigestion with some upper abdominal distress and one case, shortly after the study, was erroneously explored for perforated ulcer. In all cases while the secretory chemistry varied, there was a definite increased neutralization power as shown by the curves. Graph II in Figure 3 illustrates some of the curves. Since this is the direct opposite tendency to that found in ulcer and pylorospasm, it suggests a definite differential diagnostic test even though eight cases are not enough to substantiate conclusions.

ALLERGIC DISEASE

It was reasonable to presuppose that something of value would likely result from a study of allergic individuals especially those harboring a definitely proven food allergy. Thirty-two such cases were selected, being composed of chronic urticaria, eight; perennial hay fever, two; Migraine, one; chronic generalized eczema, three; and bronchial asthma, eighteen. All cases were proven to manifest aggravation of symptoms by certain foods or gastro-intestinal stasis. Secretory and neutralization studies were then carried out and, while the secretory chemistry fluctuated considerably with a surprising number showing achlorhydria, the neutralization curves were all within normal limits with some tendency toward an increased neutralizing power. One case ((1) Figure 4, Graph I) is of particular interest since upon the first study she showed complete achlorhydria with increased neutralizing power. Eight months later her secretory curve returned to a high normal but the neutralizing curve remained practically identical with that of the first.

MISCELLANEOUS GROUP

Thirteen cases representing different diseases but manifesting in association some indigestion and abdominal complaint, were chosen and studied. They included Acne Rosacae, one; Undulant fever, one; chronic generalized Psoriasis, one; Pellagra with diarrhea, one; essential hypertension, one; chronic appendicitis and ovarian cyst, one; tuberculosis (incipient, renal and intestinal), three; hypertrophic arthritis, four. Nothing of diagnostic value was revealed in either the secretory or neutralization curves except in the case of pellagra (Figure 4, Graph II, Case 1) in which the neutralization curve sharply dropped to zero in ten minutes and in the case of chronic appendicitis and ovarian cyst, confirmed by surgery, (Case 2) a neutralizing curve which was delayed and similar to those established by Levy.

GENERAL DISCUSSION

At the beginning of this study it was thought that a more or less untried test of gastric or gastro-duodenal function, namely the power of the stomach to neutralize 0.5% HCl when instilled into its lumen, may be of diagnostic or pathogenetic clinical value in disease in general or at least gastro-intestinal conditions other than spasm or ulcer as already established by Elman and McLeod and Levy. Especially might this be expected in allergic disease where food and gastro-intestinal upsets definitely produce or aggravate the symptoms. This study and report fails to confirm the original thought, except in cases of liver and gall bladder disease, where it has shown in a small group of proven cases that there is apparently an increased neutralizing power of the stomach, which, if confirmed, will serve as a valuable diagnostic aid since it was constant whether or not stones were present. The marked increase in neutralizing power in the case of Pellagra suggests further work as to its value in other deficiency diseases since recent reports are appearing which suggest a gastric factor in these diseases.

It is evident that the automatic regulation of acidity by the stomach is becoming one of the most important problems of physiology and gastric pathology. Since the original work of Heidenhain and Pavlov many theories have been advanced. There is no agreement as yet, and three or four opposing views exist in recent literature. Undoubtedly, the original physiological work was stimulated by the question, "Why does not the stomach digest itself?" This would be a logical question to follow the monumental work of Claude Bernard in 1856.

Modern views of the mechanism of neutralization include: (1) cessation or inhibition of HCl secretion, (2) acceleration of the emptying time of the stomach with associated secretion of a less concentrated juice, (3) mucus and acid binding substances, (4) alkaline secreted gastric juice, (5) duodenal regurgitation, (6) resorption of the secreted or introduced HCl by certain portions of the stomach.

Of these various views, undoubtedly, the most widely supported is that of regurgitation of duodenal contents. This theory was first sponsored by Boldy-

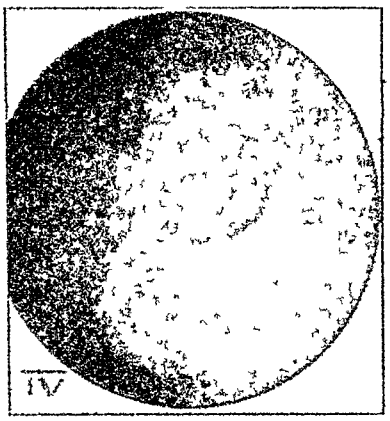


Fig. 1 is that of a single polyp.

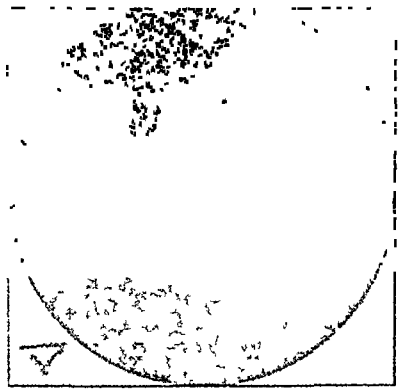


Fig. 5 shows multiple polypi, an unusual finding in the stomach. (Thanks are given to Dr. Wallace for this print).

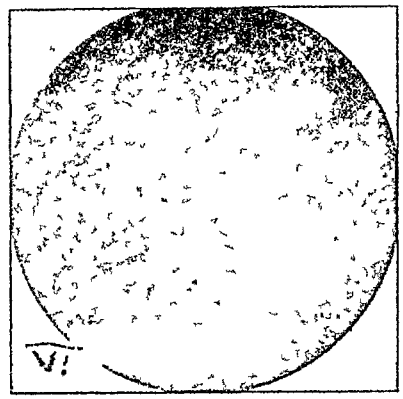


Fig. 6 shows many small erosions or ulcerations.

diagnosis, a more enlightening concept of living pathology as shown by photography is placed at the physician's disposal. It does not seem as yet advisable to speak of percentages of correct diagnosis in evaluating the benefits to be derived from the use of this procedure. The author is inclined rather to confine himself to the criteria for diagnosis, the pitfalls to be avoided and the possibilities for aid to be derived therefrom. In studying the gastric mucosa, one must remember that he is looking at photographic impressions produced by the elevations and depressions within it. The size of the deformities and irregularities seen on the completed prints are roughly, one-half the actual size. The trained physician familiar with the morphologic appearance of the normal mucosa, readily recognizes (the appearance of the rugal folds in the photograph) as they course along the stomach wall. They are higher, more compact and more numerous on the lesser curvature and flatter and sparser in other areas. An abrupt and even gradual departure from the normal becomes apparent and diagnostic conclusions readily drawn. The author presents eight photographs which demonstrate certain observations

COMMENT

Intragastric photography now has been used about seven years. Close observation and study by the author over a period of more than six years lead him to continued enthusiasm for the great possibilities of the method in an endeavor to make more thorough diagnosis of gastric lesions. Pathology may be seen on the photographic films which has been missed by X-ray studies. One is better oriented as to the pathologic histology of such a lesion when seen by this method. The possibilities for errors of omission particularly are lessened after the stomach mucosa has been photographed in addition to all other diagnostic procedures used. Its ease of application and the small amount of time consumed (usually less than one minute) makes it more desirable than gastroscopy. Then, too, one can study at leisure the permanent record of what one might more or less fleetingly see by gastroscopy. Progress has been made in the study of the application and value of the method and much more will naturally be learned concerning both the technique and evaluation of what we see, as its use becomes widespread

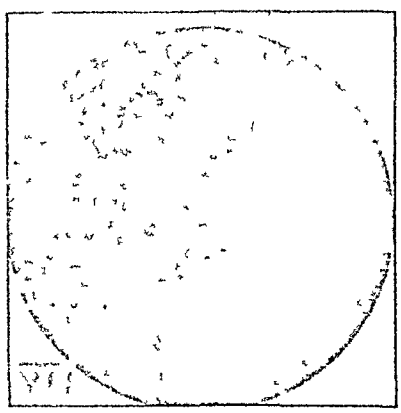


Fig. 7 is a view into and through the pyloric antrum with the pylorus itself in the distance.

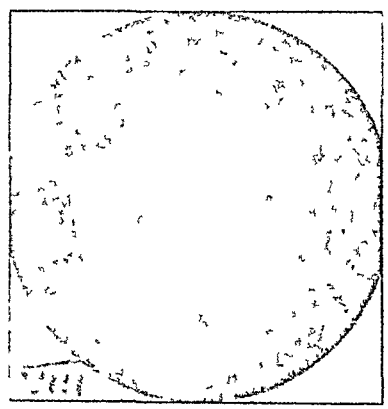


Fig. 8 is that of a hand taken at 2 inch photographic distance to convey some idea of the extent of stomach wall photographed and a comparative study as to the size of objects seen

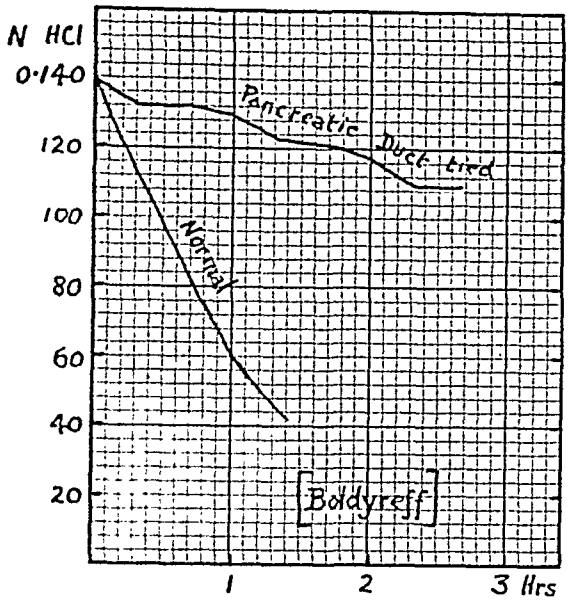


Fig. 1. Showing reduction of acidity when 0.140 N HCl is placed in a dog's stomach (a) under normal conditions, and (b) after ligature of pancreatic duct. (Redrawn from Boldyreff's figures).

delayed reduction of acidity when acid was artifically placed in the stomachs of people who had hyperchlorhydria with the ordinary gruel-meal test (Apperly 1). Fig. 2 shows the gruel-meal acidity curves of a group of eight students, and Fig. 3 shows the results in the same group when 250 c.c. of 0.4% HCl was placed in their stomachs. It will be seen that, in general, those who have high (or low) acidity in the former also have high (or low) acidity in the latter. In other words gastric acidity is a matter of dilution and neutralization rather than of secretion of acid. In the same year Apperly and Cameron (4) showed a similar failure to reduce acid placed in the stomach in cases

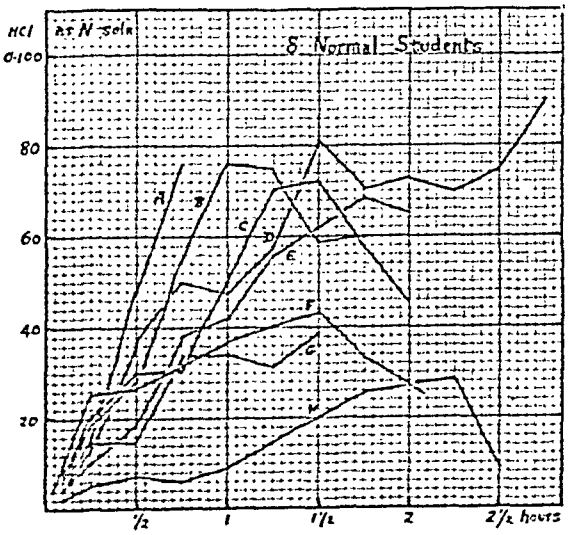


Fig. 2. Fractional test-meal curves (gruel meal) in eight normal students.

of known pancreatic disease (Fig. 4) and first suggested the "acid test" for disease of this organ. Favorable reports concerning this test have since been received. In 1924 I (2) also showed the rapid reduction in the acid test following gastro-enterostomy. (Fig. 5).

Very little further use was made of this test until 1929 when Elman (9) showed that in duodenal ulcer there is some failure to reduce acid in the stomach (Fig. 6—Compare this with Fig. 5). In 1935 he published a further series of cases of duodenal ulcer before and after gastro-enterostomy.

Levy (13) in 1934 showed among other things a diminished acid reduction in cases of chronic appendicitis before operation. (Fig. 7). He believes this failure to reduce acid is due to pyloric spasm. He

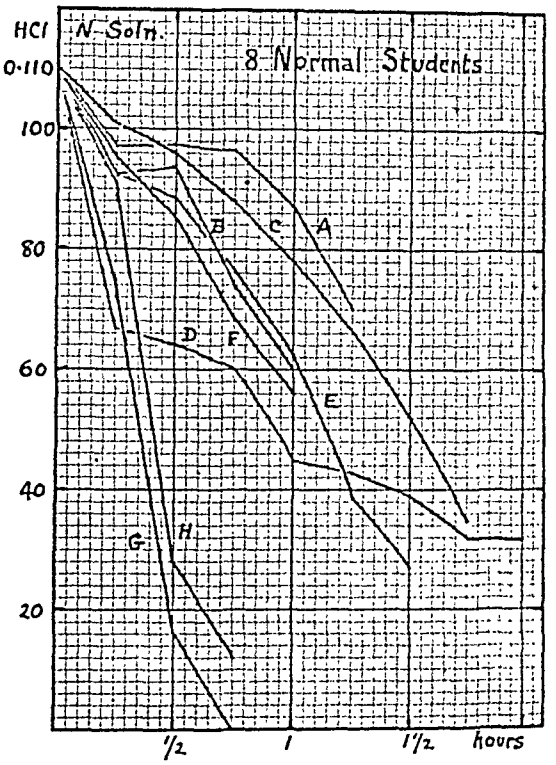


Fig. 3. Showing the fall of acidity in eight normal students (same as those of Fig. 2) when 250 c.c. of 0.110 N HCl is substituted for the gruel meal.

concluded that "as compared with the ..... Ewald test-meal, the neutralization test showed a greater uniformity and in general a closer correlation with the physical and clinical findings and would seem, therefore, to be of greater diagnostic importance."

Various writers have referred to this test as the Neutralization Test. This is a misnomer, since it has been shown by several authors (Apperly (3), MacLean and Griffiths (14) and others) that acid placed in the stomach is reduced almost wholly by dilution, and to only a small extent (and often not at all) by neutralization by duodenal fluids. Hence the term "Acidity Reduction Test" would appear to be better.

One further point should be noted. Most of those

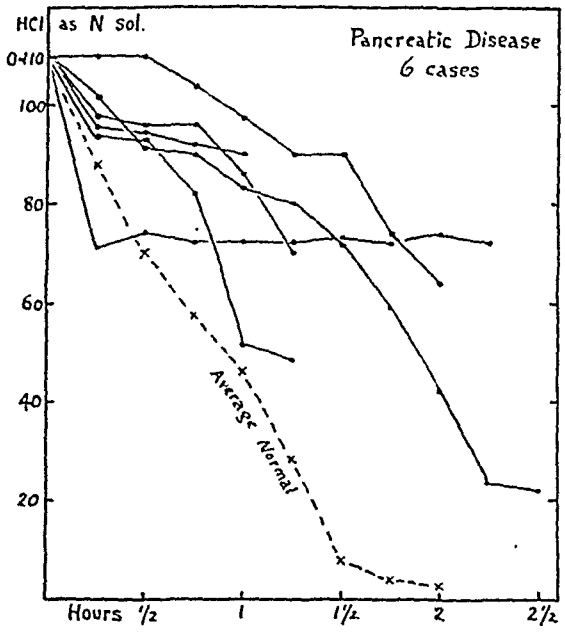


Fig. 4. Acidity Reduction Test in pancreatic disease.

using the test have assumed, following Pavlov (15), Ivy and Whitlow (12), and MacLean and Griffiths (14), that, when acid is artificially placed in the stomach, secretion of hydrochloric acid by the gastric mucosa is suppressed. Generally this appears to be true, but in a certain proportion of cases considerable additional acid may be secreted (Apperly and Norris (7)). In practice, however, this does not seem to vitiate the general results of the test.

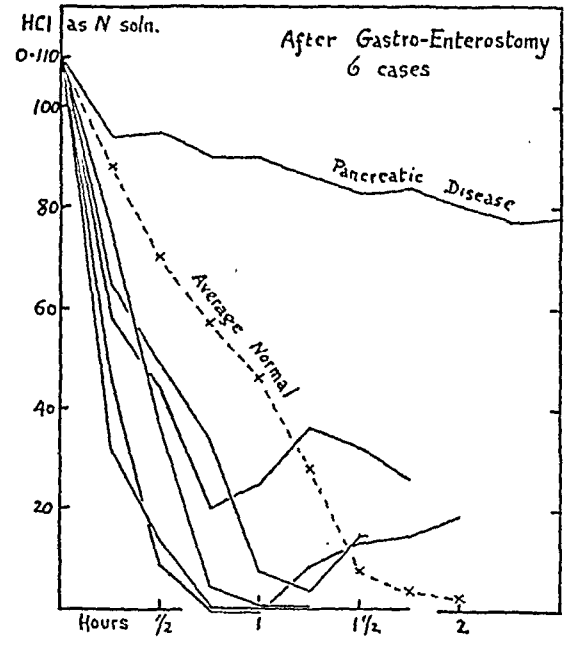


Fig. 5. Acidity Reduction Test After Gastro-enterostomy (one of these cases was found to have pancreatic disease. See Reference 2).

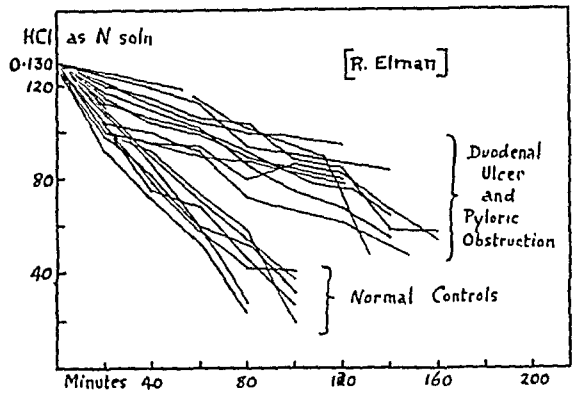


Fig. 6. Acidity Reduction Test in duodenal ulcer and pyloric obstruction. (After Elman (9)).

TECHNIQUE OF TEST

The Rehfuss tube is swallowed by the fasting patient and all fasting contents withdrawn. 250 c.c. of 0.4% (0.110 N) HCl, previously warmed to body temperature, is drawn up into a large (100 c.c.) pipette, which is then attached to the free end of the tube. By holding the pipette above the level of the head, the acid runs into the stomach by gravitation. The test is then conducted as in the usual fractional test-meal, i.e. samples are withdrawn every ¼ hour and titrated for free acid. Insufficient stress however has been laid on one very important point, viz., thoroughly mixing the gastric acid before withdrawing a sample, by moving the piston of the withdrawing syringe back and forth about 6 or 8 times. Experience has shown that this insures a uniform mixture in the stomach.

DISCUSSION

The degree of acidity of the gastric contents does not, of itself, give rise to any sensation. Thus acid, of an acidity far greater than that found in any pathological condition, when placed in the stomach is not in any way appreciated. On the contrary, Hurst (11) has shown that the only adequate stimulus for the production of the sensations of fullness, discomfort and pain in the stomach and intestine is increase of ten-

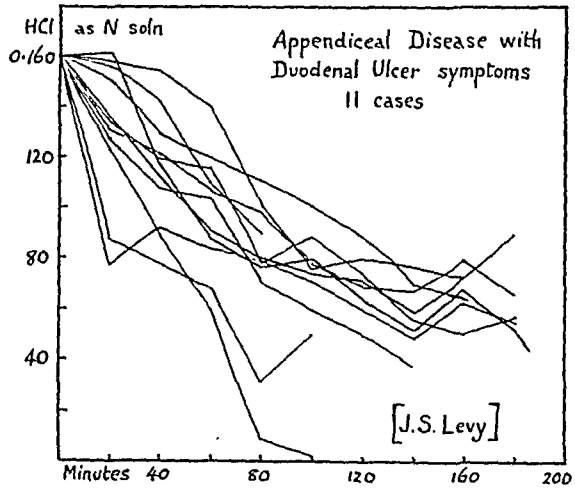


Fig. 7. Acidity Reduction Test in appendiceal disease with ulcer symptoms. (After Levy (13)).

sion or pressure of contents above a certain critical level in that organ. Thermal, chemical, or tactile stimuli, provided they do not cause spasm and rise of tension, are not felt by the patient. This has been shown in operations under local anesthesia.

From the foregoing facts it follows that these symptoms of indigestion can be brought about by such incoordinations of gastro-intestinal muscular activity as give rise to increased intra-gastric or intra-intestinal pressure. Thus a stomach powerfully forcing its contents against a pyloric obstruction gives rise to fullness, discomfort or pain according to the degree of pressure produced.

On the other hand we know from common experience that high or low acidity is often found in certain different forms of indigestion—but not necessarily. In order to clearly understand the relation of acidity to gastro-intestinal muscle function let us consider the series of events following a meal.

When a gruel test-meal is placed in the stomach, hydrochloric acid of concentration 0.174 N (Hollander and Cowgill (10)) is secreted into the fluid food. Usually the acidity rises for one to 1¼ hours and then falls. This fall is brought about chiefly by a regurgitation of duodenal fluids which dilute and to some extent neutralize the gastric acid. The acidity curve can be raised by: (a) increased secretion of acid. (b) increased rate of gastric emptying, which leaves a smaller residue of food to be acidified, thus raising the concentration of the acid, and (c) a diminution or failure of duodenal regurgitation. An opposite set of conditions lowers acidity.

With this double response of the stomach to the introduction of food, viz. 1. acid secretion, and 2. gastro-intestinal movements of flux and reflux, it is obvious that if we could eliminate the former, then any variations in the acidity curve must be brought about wholly by the latter, and so give a much clearer indication of the nature of the faulty gastro-intestinal muscle activity, which is the cause of the symptoms. Hence the origin of the Acidity Reduction Test. In fact, by substituting hydrochloric acid for the Ewald meal, we eliminate both (a) and (b) above.

The figures shown demonstrate these faulty mechanisms. Thus there is a retardation of acid reduction in cases of pyloric obstruction or spasm (Figs. 6 and 7) and in cases of insufficient production of pancreatic alkali, whether brought about experimentally (Fig. 1) or by disease of the pancreas (Fig. 4). Norris and I (7) also showed a retarded rate of reduction in chronic nephritis and in diabetes, two diseases commonly associated with a diminished blood alkali reserve, which in turn brings about a diminished secretion of pancreatic alkali. In all of these cases there is delayed emptying. Even in cases of rapidly emptying hypertonic stomachs, in which flux dominates over reflux, I have found that the acid remains high.

Conversely, when reflux or regurgitation is facilitated, as by gastro-enterostomy (Fig. 5) or where there is an abundant secretion of alkali (Apperly and Crabtree (6)), the stomach empties rapidly with a sharp fall in the acid curve (shown in some cases in Fig. 3).

I have found no definite deviation from the normal in patients with gall bladder disease or with achylia gastrica.

Some other physiological factors governing this test have been discussed elsewhere (Apperly and Cary (5)).

CONCLUSION

From experimental and clinical evidence it is concluded that the Acidity Reduction Test is superior to the gruel or Ewald fractional test-meal.

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The Relation Between the Acid-Base Equilibrium and the Gastric Bacterial Flora*

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and

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BACTERIA are continuously being introduced into the body, from the air, from food, and in countless ways in which the lips come in contact with non-sterile surfaces. For the most part these organisms are non-pathogenic and apparently exert little or no influence on the body. Under certain conditions, however, pathogenic organisms are the contaminants, and disease may or may not result, depending upon the ability of these organisms to become established in the body. Such power is due not only to the virulence or adaptability of the exogenous flora, but also to the break down in the various mechanisms by which the body is able to protect itself. This present work is a study of one of the protective mechanisms by which the body defends itself against this entrance.

All of the experiments were performed on patients in the medical wards of the Research and Educational Hospital of the University of Illinois, College of Medicine. Although none of these persons could be considered entirely normal from a health standpoint, those exhibiting any particular dysfunction of the gastro-intestinal tract or suffering from primary anemias were not used. Patients showing relatively low gastric acidity were chosen for many of the experiments. This was necessary in as much as this work was concerned with bacterial growths which usually are associated with this type of gastric contents. No doubt such cases were more frequent in this hospital population than would be in a normal cross section of healthy adults. Several series of experiments reported by Davies and James (1930), Vanzant, Alvarez, et al (1932) and Bloomfield and Keefer (1928) showed that there is a consistently higher percentage of true as well as apparent cases of achlorhydria in individuals with advancing years. The latter group of workers showed that this anacidity was proportional to the lowering of physical fitness although the conditions were apparently unrelated to disease of the gastro-intestinal tract.

A series of six experiments were carried out to show the relation of the hydrogen-ion concentration to the bacterial growth of the stomach.

Experiment I: The Relation of Hydrogen-Ion Concentration to Bacterial Growth.

In this experiment aspirations by means of Rehfuss tubes were made from the fasting stomachs of a group of 106 patients. The hydrogen-ion concentration was determined by a colorimetric method and bacterial growth by plating out one standard loop of material on the surface of plain agar. Although there were a few marked discrepancies the following table shows the general relation between hydrogen-ion concentration and bacterial growth in human gastric contents. Graph I shows the actual values.

Less than pH 1.0	Sterile.
Between pH 1.0 and 2.0	Occasional colony.
pH 3.0	Borderline of bacterial growth.
Above pH 3.0	Heavy bacterial growth.

This corresponds in general to the results reported by Bartle and Harkins (1925) and Gregerson (1916).

Experiment II: Changes in Hydrogen-Ion Concentration and Bacterial Flora of the Stomach During a Period of Three and One-Half Hours.

The Rehfuss tube was inserted and control aspirations were obtained from the fasting stomach of five patients. Each subject was permitted to eat breakfast with the tube in place. Aspirations were then made at fifteen minute intervals for two and one-half to three and one-half hours. Cultures and hydrogen-ion determinations were taken on each sample to show the relationship between the acid-base equilibrium and viable bacterial flora over a period of several hours. The increased concentration of hydrogen-ions within the gastric contents was associated with a decrease in the viable bacterial flora following in general the relationship noted in Experiment I. Graph II demonstrates this fact. Similar results are reported by Johnson and Arnold (1932) and Nedzel and Arnold (1932).

Experiment III: The Influence on the Hydrogen-Ion Concentration and the Viable Bacterial Flora Produced by the Introduction of Acid or Alkali into the Stomach.

The Rehfuss tube was inserted and a control aspiration was obtained from the fasting stomach of each of nine patients. This material was cultured and the hydrogen-ion concentration determined. If the reaction was more alkaline than pH 3.5, 50 c.c. of 1 per cent hydrochloric acid were added; if more acid than pH 3.5, 50 c.c. of phosphate buffered alkali were added. After five minutes a second aspiration was made and treated as the first fraction. With the shifting of the pH of the stomach contents because of the addition of the acid or alkali there appeared a corresponding change in the abundance of growth of the gastric flora. In this series of nine cases and in others reported elsewhere, the response to the acid was much more readily obtained than was a similar response to the alkali. (See Graph III).

Experiment IV: The Influence on the Hydrogen-Ion Concentration and the Viable Bacterial Flora Produced by the Introduction of Organic Acids into the Stomach.

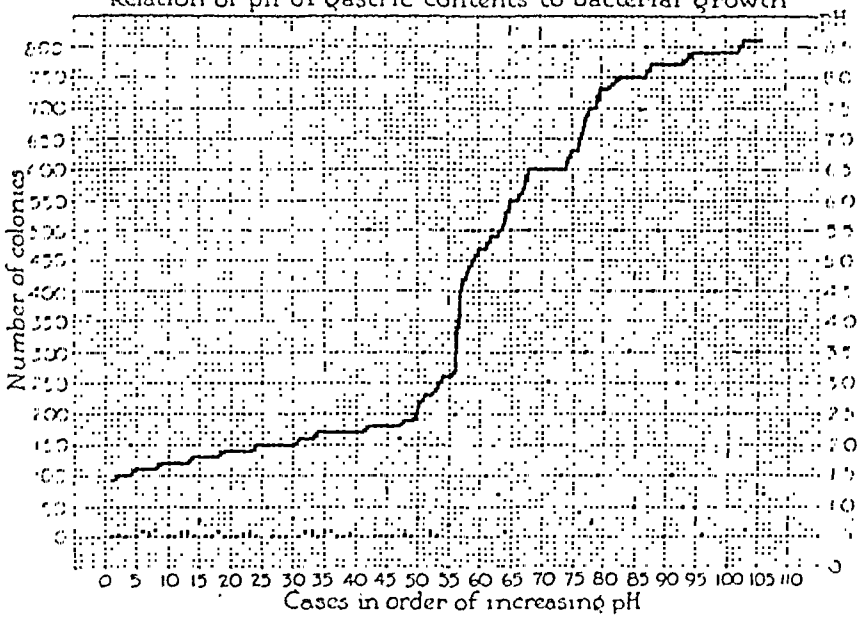
Various organic acids were substituted for the mineral acid of Experiment III to find whether or not these would exert a similar influence upon the hydrogen-ion concen-

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Graph I

Relation of pH of gastric contents to bacterial growth



tration and viable bacterial flora of the stomach. A Rehfuss tube was inserted into the fasting stomach of each of three patients and control aspirations were made. Fifty cubic centimeters of 1 per cent hydrochloric acid were introduced and five minutes later were aspirated. On four succeeding days the above experiment was repeated, substituting similar amounts of various organic acids for the mineral one first used. Cultures and hydrogen-ion determinations were made on each specimen and the results are shown on Graph IV.

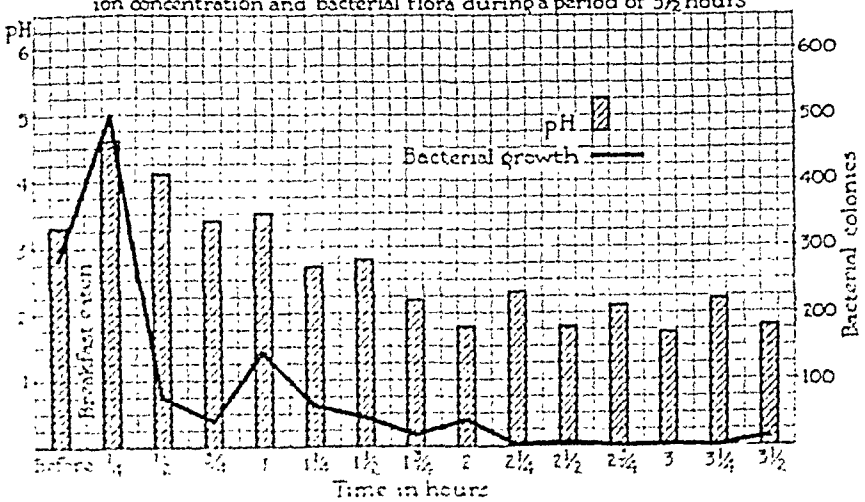
In this series of cases the lemon juice appeared to be as efficient in acidifying gastric contents and thereby rendering many of the organisms non-viable as an equal amount of 1 per cent hydrochloric acid. In an *in vitro* experiment Knott (1923) found the organic acids very deficient in germicidal power. Kugelmass (1935) reported a series of cases where fruit juices were given to children. He found that fruit juices fluctuating about pH 3.0 stimulated, within the first fifteen minutes after ingestion, a gastric pH of about 3.5. The titration curves showed that the juices are mixtures of weak acids and their salts, containing small amounts of free acids. The presence of free acid was shown by Clark (1915) to be the determining factor of bactericidal power.

Experiment V: The Length of Time the Fasting Stomach Retains Acquired Acidity.

Experiments III and IV show that the addition of acid, either mineral or organic, affects the acid-base balance of the stomach with a comparable change in the number of microorganisms which can be cultured from the contents.

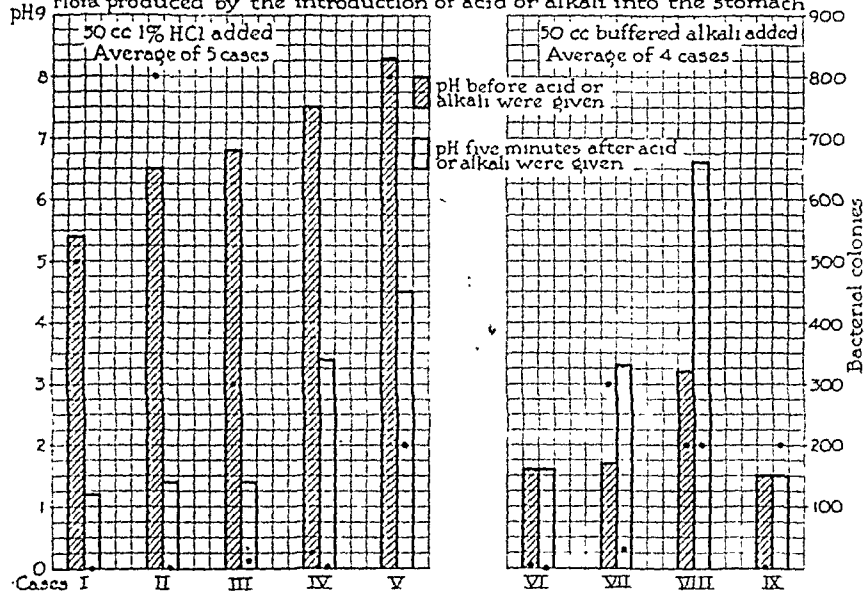
Graph II

Average taken from five cases showing changes in hydrogen ion concentration and bacterial flora during a period of 3½ hours



Graph III

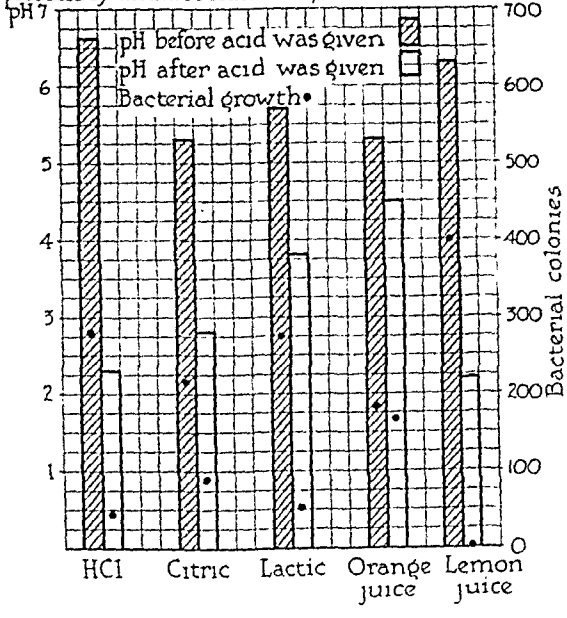
The influence on the hydrogen ion concentration and the viable bacterial flora produced by the introduction of acid or alkali into the stomach



In a series of five cases aspirations were made by means of Rehfuss tubes inserted into the fasting stomachs. Cultures and hydrogen-ion determinations were taken on these and all subsequent fractions. Fifty cubic centimeters of dilute hydrochloric acid of pH 1.2 were then introduced through the tubes. Aspirations were made at fifteen minute intervals until the reaction approached or equaled the original pH value. This is shown on Graph V. The stomachs of these five patients retained the acquired acidity for approximately one and one-half hours or sufficiently long to aid the action of the peptic enzyme and to give protection against bacteria which may be introduced during the digestive period. Boldyreff (1914), using one man and four dogs reported a return to normal acidity in from forty-five to sixty minutes.

Graph IV

Average of three cases showing the influence on the hydrogen ion concentration and the viable bacterial flora produced by the introduction of organic acid into the stomach

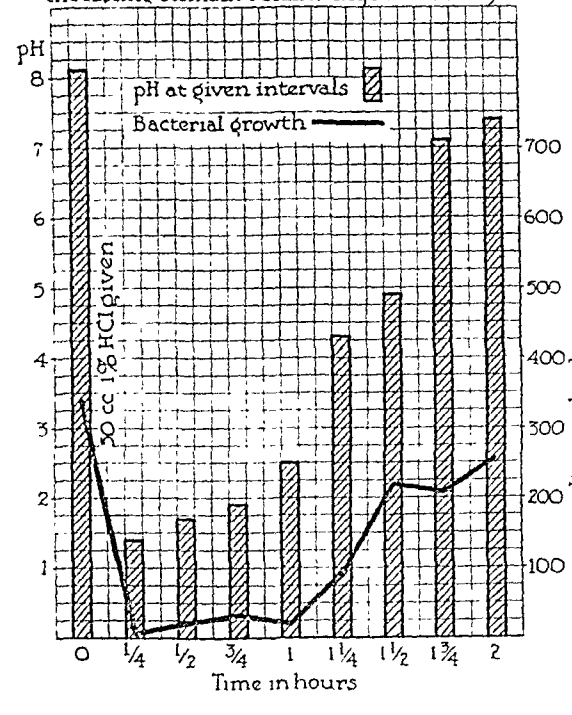


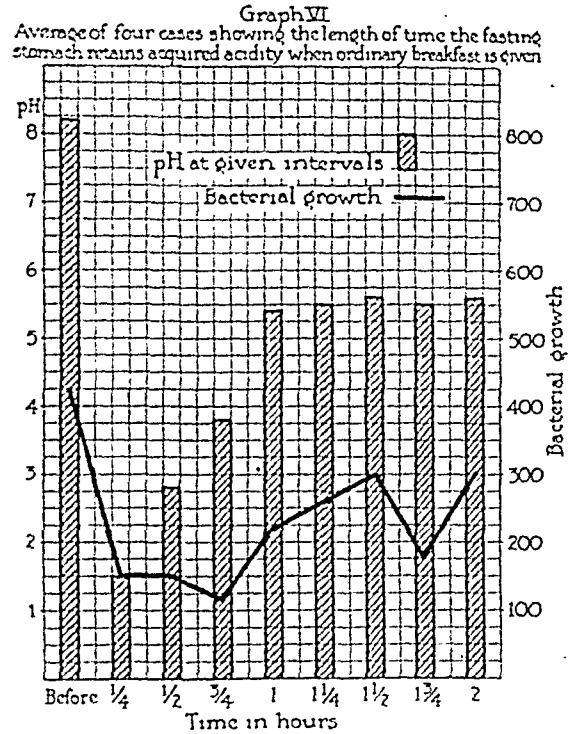
Experiment VI: The Length of Time the Stomach Retains Acquired Acidity After a Normal Breakfast is Ingested.

To be of physiological importance this change in reaction must be effective when food is taken into the stomach.

Graph V

Average of five cases showing the length of time the fasting stomach retains acquired acidity





Two patients, showing anacidity in the control aspirations, were chosen for a series of tests to show whether or not the addition of food shortened the period of activity of the introduced acid. Under fasting conditions Case I showed retention of acquired acidity for a period of more than two hours. With the addition of a normal breakfast this time was approximately one hour. The addition of food in Case II reduced the period of acid retention from one and one-half hours to three-quarters of an hour. The results are shown in Graph V. The explanation lies in the fact that part of the acid combines with the food leaving a smaller amount of free or effective acid present. Much the same conclusion was drawn by Cornwall and Le Frenais (1921) who found the total acid greater after a test meal because the food stimulated the gastric glands to greater secretory activity. The free acid was decreased in amount because much of it went into combination with the ingested food.

DISCUSSION

Bacterial growth in general parallels the acidity of the gastric contents. This was shown by cultures of gastric material taken from 106 cases reported in Experiment I. The borderline for growth was about pH 3.0. Cultures of gastric contents showing acidity above this value were, for the most part, sterile and those of lesser acidity produced abundant growth. Thus the hydrogen-ion concentration of the normal stomach which varies around pH 2.0 has the power of rendering viable bacteria non-viable and therefore aids in protecting the body from intragastric contact with living bacteria. It was shown by following the course of digestion for a three and one-half hour period, that the acidity of the normal stomach is not a brief phase in the digestive cycle to be followed by low acidity with consequent lack of protection, but that it maintains itself throughout the intradigestive phase. Fasting stomachs that have relatively low acidity but normal secretory power produce sufficient acid during digestion to retain the protective power over a period equal to the normal time between meals.

Experiment III showed that it is a relatively easy matter to change the reaction of gastric contents from that of neutrality or alkalinity to acidity by the addition of comparatively small amounts of dilute hydrochloric acid (50 c.c. of 1 per cent hydrochloric acid). This is significant for the large group of apparently normal people who have hypo-or anacidity and thus have a densely populated bacterial flora in the lumen of the stomach. The acquired acidity was retained by the fasting stomach for approximately one and one-half hours. When a normal breakfast was eaten following the administration of the acid, the change in pH was retained for a shorter period of approximately three-quarters of an hour. During this period of artifically produced acid gastric contents the patient maintains a normal gastric flora.

This protective action may be brought about by substituting 50 c.c. of 1 per cent organic acids for the dilute hydrochloric acid if the resulting hydrogen-ion concentration is below pH 3.0. The juice of one-half lemon in 50 c.c. of water proved to be the most effective acid used although the initial pH was not more acid than that of the citric or lactic acids employed. Thus the old idea of giving lemon juice in cases of gastro-intestinal disturbances when anacidity was suspected is substantiated.

To render a naturally acid stomach alkaline is a much more difficult procedure. The addition of the alkali apparently excites the glands to greater activity so the resulting reaction is the same or only slightly more alkaline.

CONCLUSIONS

1. Cultures of the contents of fasting stomachs showed a bacterial growth that paralleled the hydrogen-ion concentration of this material in approximately the following manner:

Less than pH 1.0	Sterile.
Between pH 1.0 and 2.0	Occasional colony.
pH 3.0	Borderline of bacterial growth.
Above pH 3.0	Heavy Bacterial growth.

2. Continuing the observations over a three and one-half hour period showed a variation in hydrogen-ion concentration. This was associated with a parallel change in the viable bacterial flora.

3. The alterations in the hydrogen-ion concentration of the gastric contents produced by the ingestion of dilute mineral or organic acids were associated with a decrease in the viable bacteria flora. The ingestion of buffered alkaline solutions were associated with an increase in the viable gastric flora.

4. The addition of 50 c.c. of 1 per cent hydrochloric acid to the fasting stomach shows a retention of free acid for approximately one and one-half hours. This period was reduced to somewhat less than one hour if food was ingested.

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Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer*

By

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THE purpose of this paper is to report briefly the results obtained in the treatment of patients affected with X-ray positive peptic ulcer.

The patients were selected in the following manner: First, they had the complaints which lead one to suspect the presence of a peptic ulcer, and second, no matter how suggestive these complaints, their histories and physical findings may have been, they were not, with the exception of Case 19, admitted to this group unless there was positive X-ray evidence of peptic ulcer. It is safe to assume, then, that they are all *bona fide* cases of peptic ulcer of one type or another.

The majority of these patients was from the white male outpatient or ward medical service at the Charity Hospital. Economically, for the most part, the subjects were from the lowest level, though some living in the country have the good fortune to be able to obtain a wide variety of dairy and other farm products suitable for use in a soft diet. The Creole cooking, which is the normal diet of these patients, while it is delectable beyond words to the normal individual, is about as far removed from what a person suffering from peptic ulcer should eat as any diet one can imagine. A soft diet for our patients means much more of a change of dietary habit than does a soft diet for a Northern patient, whose normal diet is relatively bland and free from strong seasoning substances.

In considering the possibility of giving these patients any appreciable amount of rest, it was at once seen to be impossible, for those who had any sort of job did not dare let it go, and those who were not employed could not be given bed rest in the Hospital due to crowded conditions incident to the demolition and reconstruction of a large portion of the institution. The few patients who were admitted directly to the wards were regarded as ambulatory and were allowed to be up and around during the day and were given improvised beds of blankets on the floor at night. Home conditions were such that no more than the most meager limitation of activity could be obtained. As examples of the degree to which activity could be limited let me cite two cases: A man who was accustomed to operate a pneumatic riveter had his job changed to operating an acetylene torch; another who did the heavy pulling necessary in recovering a large fishing net was able to change to some of the less arduous duties of a commercial fisherman. I think from these instances it is clear that the ordinary benefits obtained by a "rest cure" were negligible. The predominating nationalities of the patients are French and Spanish. The high strung temperament and often emotional instability which is inherent in people of such descent may predispose to ulcer and is an added difficulty in an attempt to obtain improvement after the ulcer is present.

The methods of treatment of peptic ulcer are almost without number, and of every method there are countless modifications. Diet regulation, rest and neutralization of acidity stand out as important factors in almost all instances. The multiplicity of treatments is not necessarily to be deplored for though it indicates the lack of a specific, one type or form of treatment may aid in the attainment of remission in a given case that has been or would be unaided by any of several other methods or modifications thereof. It is not my purpose to add a method to the many now in existence, but merely to record some rather favorable results in a group of peptic ulcer patients treated with aluminum hydroxide.

B. B. Crohn (1), in 1929, was the first to report on the use of aluminum hydroxide in this country. Einsel and Rowland (2) reported, in 1932, on the use of aluminum hydroxide, both in the colloidal form and in a non-colloidal form, but since the latter form had no appreciable acid-combining power, they abandoned it for the colloidal preparation which seemed to have a very good acid-combining power. Einsel, Adams and Myers (3) reported 110 patients with peptic ulcer treated with colloidal aluminum hydroxide, with but 8 per cent failures. The treatment consisted of six feedings per day followed in 30 to 60 minutes by 4 to 12 c.c. of a gelatinous preparation of colloidal aluminum hydroxide. Woldman and Rowland (4, 5) reported on the use of a continuous intragastric drip for the administration of a diluted colloidal aluminum hydroxide. The results obtained by this method and checked by X-ray were extremely favorable. With this method, I have had only slight experience (Case 19). Adams, Einsel and Myers (6) conclude in part that, due to the

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administration of colloidal aluminum hydroxide, there is a decrease of total amount of acid secreted by the stomach and that this total tends to become progressively lower with continued use of the drug. That this reduction of acid secretion is not due to permanent damage to secreting cells is indicated by the fact that even after several months of treatment, histamine injections give the same acid response that was obtained previous to treatment. After many months of continuous administration of aluminum hydroxide there is no significant change in serum calcium, total base or carbon dioxide content of the blood.

It seems that the following facts are established. Aluminum is not absorbed from the intestinal tract to any significant extent. Aluminum hydroxide taken by mouth has no effect on the acid-base equilibrium of the blood. The preparation of colloidal aluminum hydroxide used in these cases has an acid-combining power of 15 to 16 volumes of tenth normal hydrochloric acid. The dosage used varied from 4 c.c. three times a day to 8 c.c. four times a day, taken after meals and at bedtime. An ordinary soft diet was given in conjunction with the drug. A few cases were given 0.3 gm. sodium bromide and 2 c.c. tincture hyoscyamus three times a day and a few were given mineral oil as their bowel habits required. No two hour or hourly feedings, no alkalies and no injections of any kind were used in any of this series of cases.

AUTHOR'S STUDY

In this group there are 22 males and two females, the average age being 42 years, ranging from 12 to 64, with about equal distribution in the third, fourth, fifth, sixth and seventh decades. In ten cases the symptoms had been present less than one year, averaging six months. In 12 cases the symptoms had been present over a year, averaging seven years. The most common complaint was epigastric pain definitely related to meals. Well localized epigastric tenderness was present in almost all cases.

TABLE I

No.	Age	Duration	Location	Symptoms Relieved in*	Re-Ray Following Treatment*		
					Pos.	Neg.	Improvement
1	12	4 mos.	G			41	
2	46	2.5 yrs.	G	2		21	
3	48	6 yrs.	D	2		19	
4	52	5 mos.	D	1		7	
5	22	6 mos.	G	3		34	
6	64	5 yrs.	D	1		18	
7	56	6 mos.	D	3		35	
8	20	4 mos.	D	5		21	
9	32	4 mos.	D	4	12		
10	61	6 yrs.	D—AP	2			Scar deformity
11	52	?	G—AP	4			Marked 48 days
12	32	10 mos.	G	4	not done	not done	
13	31	1 yr.	G—AP			32	
14	50	20 yrs.	D				Slight 60 days
15	28	2 yrs.	D			31	
16	32	?	D	2		38	
17	39	8 mos.	G—AP	2	not done	not done	
18	63	7 yrs.	D	4		56	
19	33	2 mos.	?	4	not done	not done	
20	38	2 yrs.	G	5	not done	35	
21	28	11 yrs.	D	1		not done	
22	60	10 yrs.	D	2	not done	not done	
23	48	10 mos.	D	3	not done	not done	
24	50	3 yrs.	D	6	not done	not done	

* Time recorded in days
G = Gastric
D = Duodenal
AP = Accessory pocket

Immediate results were as satisfactory in the chronic cases as in the acute ones except that the only case in which the radiologic evidence of healing was not entirely satisfactory after a reasonable length of time (60 days) was a man who had had the disease for 20 years.

The following cases have been selected because they illustrate the various types of cases seen in this group. Case 1 is presented largely because of his age.

Case 1. W. S., a white male, aged 12, was seen April, 1936, complaining of post-prandial pain of four months' duration, relieved by sodium bicarbonate, or vomiting. He

had, however, been subject to gastro-intestinal upsets all of his life according to the statement of his mother. Fluoroscopic examination on April 27, 1936, showed an ulcer of the fundus one centimeter in diameter. His treatment was started at once, but the ordinary powders and diet failed to relieve him more than temporarily. On May 15, 1936, obtaining some colloidal aluminum hydroxide, he was given 12 c.c. three times a day, diet consisting of strained vegetables, milk products, soft boiled eggs and toast. Symptomatic improvement was noted almost at once, and he continued to improve until symptom-free on June 26, at which time there was no evidence of gastric or duodenal disease on X-ray examination. He is a well and healthy boy at the present time, gaining weight and free of gastric complaints for the first time in his life.

Case 2 is selected as being approximately the average patient except that the gastric ulcers were outnumbered by the duodenal ulcers.

Case 2. D. R., aged 46, was re-admitted to the hospital on August 11, 1936, complaining of epigastric pain of two and a half years' duration, three or four hours after the noonday meal. The pain was followed by nausea and vomiting which gave relief. He had been a patient in the same ward in March, 1936, at which time his X-ray showed an ulcer 4 by 7 mm. on the lesser gastric curvature. This finding was also present on August 13. Epigastric tenderness was present, and his gastric analysis showed 45° free and 82° total acid. He had a slight secondary anemia. Starting on August 20, he was given colloidal aluminum hydroxide, 4 c.c. three times a day along with a soft diet. After two days he had no further pain or discomfort. On September 10, or 21 days after treatment was initiated, he had a normal fluoroscopic examination. He remains well to the present time and has practically discontinued the medication.

Case 4 is presented because of the extremely rapid loss of X-ray evidence of ulcer which is not unusual in this method of treatment but for one case is naturally open to some question.

Case 4. C. M., aged 52, was admitted to the hospital on September 5, 1936, complaining of pain in the epigastrium following meals, which had occurred after every meal for the last three months and for the two months previous had occurred with increasing frequency. On September 10, a duodenal cap ulcer with crater formation was demonstrated by fluoroscopic examination. Gastric contents showed free hydrochloric acid 63°, total 72°. On September 12, aluminum hydroxide therapy was instituted along with a soft diet. He was relieved of pain at once, and on September 19, or seven days after treatment was started, he had a fluoroscopic examination that showed no abnormality of stomach or cap. Six months later he had gained weight and was feeling in perfect health.

Case 11 is presented to illustrate the healing of a gastric ulcer with an accessory pocket.

Case 11. A. G., aged 52, a fisherman by trade, was admitted to the hospital in September, and on September 24, showed an accessory pocket of a perforating ulcer above the incisura angularis with 50 per cent six hour retention. On September 26, aluminum hydroxide, 4 c.c. every third hour, was started together with a bland diet. After two weeks the aluminum hydroxide dosage was reduced to 4 c.c. three times a day. He felt well in four days and insisted on going out to the fishing grounds. The fluoroscopic examination on October 5 showed the pocket unchanged in size but not tender and on November 13, the fluoroscopic examination showed the pocket almost gone and not tender.

Case 19 is presented since it is the only severe hemorrhage case in the group and demonstrates the use of the continuous intragastric drip method of administration of colloidal aluminum hydroxide.

Case 19. C. V., a 33 year old mechanic, was admitted to the hospital on October 21, 1936. For five weeks he had had an epigastric pain which was relieved by food. Five days previous to admission he had started to become weak and pale and shortly began to pass tar-colored stools. He rapidly became so weak that he was unable to stand up and was brought to the hospital in a most depleted state. Shortly after admission there was expelled a large amount of coffee-ground vomitus. The upper portion of his abdomen was generally tender but not rigid. He was treated for shock and given a transfusion of 450 c.c. of citrated blood on the day of admission and 250 c.c. four days later. Aluminum hydroxide was started, 4 c.c. every third hour, on October 23. He received about eight such doses in the first 24 hours of aluminum hydroxide treatment and was then given the medication by a continuous intragastric drip* which was continued day and night for seven days. In this time he received between 250 and 275 c.c. daily of colloidal aluminum hydroxide diluted so as to make about a 25 per cent solution. Several aspirations through the nasal tube showed from zero to 5° of free hydrochloric, but after the first day no blood was detected. He became rather constipated but as he was getting very little food by mouth no effort was made to cause a bowel movement. After five days of the continuous drip he had a movement consisting largely of the tar colored material following which his stools remained negative for occult blood. He was up and around in 12 days after admission. The red count was 1,775,000 on the day of admission and 19 days later on discharge to the out-patient department, it was 3,505,000. On November 30, his red cell count was 5,325,000. His fluoroscopic examination the day before discharge failed to reveal an ulcer. Did the ulcer heal in that time, or was it in a position not amenable to demonstration? I do not know. Did he have an ulcer to start with? I believe he did.

SUMMARY

1. A brief abstract of the case histories selected from 24 patients affected with peptic ulcer, all of whom were treated with colloidal aluminum hydroxide, is presented.

2. All but one of the 24 patients have had complete relief of symptoms. The one exception is the patient, presented as Case 14 in the chart, who has been sick for 20 years and had only slight X-ray improvement in 60 days. Three showed a gradual relief of symptoms so that it is difficult to say in how many days they became symptom-free. The remaining 20 showed a prompt relief that could be accurately measured in days, their average time for relief of pain being 3.0 days. Only three required longer than four days. Lessening of pain always started at once upon the institution of treatment.

3. Of the 16 patients who have been re-rayed, 13 (nine duodenal and 4 gastric) showed disappearance of their ulcer in an average of 30 days. One duodenal ulcer was not improved in 12 days, while another duodenal ulcer showed improvement in 60 days. One gastric ulcer with accessory pocket formation showed improvement in 11 days and almost complete disappearance of the pocket in 49 days.

*Using an especially constructed apparatus lent by the Cleveland Chemical Associates who also furnished the colloidal aluminum hydroxide.

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A Review of Intragastric Photography

By

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IN April, 1930, Bernstein and Gray (1) described their experience with intragastric photography in twenty patients. Since then, the senior author has continued his interest in the subject and has had opportunity of observing a large number of patients, many of whom were followed up by surgery or autopsy. Since our first report, a number of articles and monographs in English, German and French have been published. It would seem of advantage to review at this time the present state of our knowledge and experience with intragastric photography.

The *instrument* used in carrying out this procedure, referred to as the "gastrophotor," has undergone considerable change in its mechanism and the photographic results obtained since its invention by Back and Heilperin of Vienna about seven years ago. Progress has been made in the refinement of technique as well as in the study of the criteria for diagnosis. Briefly described, the apparatus consists of a long tube-like affair, no thicker than the familiar Ewald stomach tube, with a double camera and a light at its end. The electric current is carried and inflation is done through the handle. There is likewise, here, an arrangement for shutter displacement. In the bulb at the tip, a bluish light of great intensity, producing no heat, is flashed on momentarily after the camera "eyes" have opened. The complete circumference of the stomach and about two-thirds of its area is seen in the sixteen pictures obtained. The location of the apparatus in the stomach is observed by fluoroscopy. Its orientation to the respective walls and curvatures is determined by cutting and loading the films in a distinguishing manner. The necessary photographic distance is obtained by moderate gastric inflation. After the films have been developed, they are enlarged, printed and studied for diagnosis.

The great value of photographically studying the gastric mucosa can scarcely be doubted, particularly after one has obtained a fleeting glimpse of it by means of a gastroscope. How much more satisfactory to be able to study the permanent record of such a view, usually obtained with such difficulty! Aschner and Berck (2) believed the method to be a valuable adjunct to diagnosis. Finkelstein (3) in 1931 and more recently again discussed his results in a large number of cases. Thal (4) and later Cunha (5) contributed to the general knowledge of the procedure and its diagnostic value. Rehfuss (6) has commented favorably; also Whigham (7) and Wyard (8) in the British literature. Rehfuss presented an exhibit of his personal experience with this procedure at the Scientific Assembly of the American Medical Association in 1935. A chapter of L. W. Kohn's "Diseases of the Digestive System." (9) has been devoted to the subject. In the French and German literature, Becart (10), Ehrenteil (11), Garin and Bernay (12), Heilperin and Porges (13) Haudek (14), Pauchet (15), and others have also contributed to our knowledge.

In the study and use of this method of intragastric

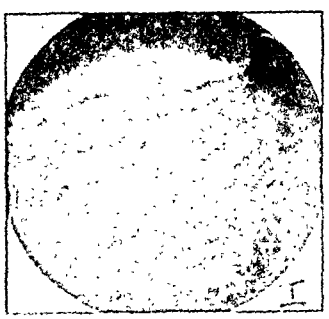


Fig. 1 is that of a normal mucous membrane. The numerous small white spots seen in many pictures are reflections from fluids sticking to the mucous membrane.

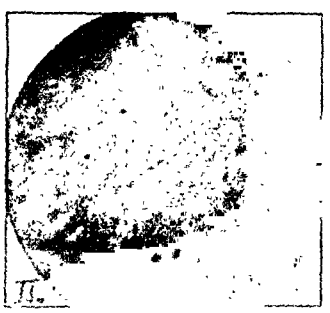
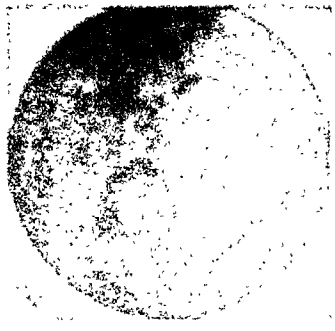


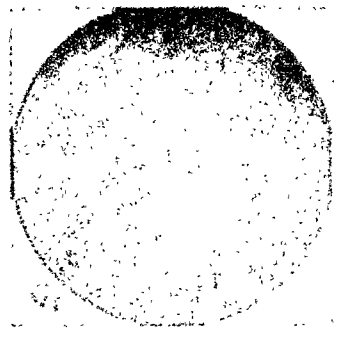
Fig. 2 is that of an ulcer-characteristic crater-like formation and raised edge.



Fig. 3 is that of a carcinoma and one readily notices the sharp demarkation and change from the normal surrounding mucosa—also the elevations and loss in normal structure.





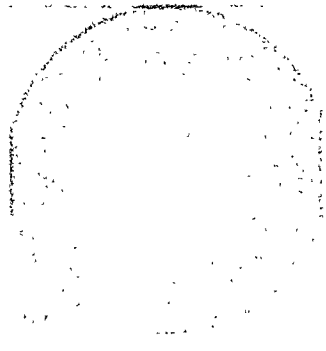


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Alcohol as a Stomachic*

By

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and

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THAT alcoholic beverages in small doses may promote gastric digestion has been known from time immemorial. The secretagogue action of alcohol on the gastric glands was discovered in the middle of the 19th century (Frerichs (3), Cl. Bernard (2)). Our present knowledge of the effect of alcohol on gastric digestion may be summarized briefly as follows (*cf.* Babkin (1)). Alcohol in dilute solution (5 to 20 per cent), introduced into any part of the digestive tract, quickly evokes a copious flow of gastric juice, which has a high acidity and a very low digestive power. When alcohol in strong concentrations is applied directly to the gastric mucosa, a profuse secretion of mucous alkaline fluid occurs; the secretion of normal gastric juice is inhibited in such cases, the inhibition lasting for several days. The fact that a weak alcoholic solution stimulates gastric secretion suggested its clinical use as a test-meal (*cf.* Katsch (4)). The alcohol test-meal was often employed, especially in Germany (under the name of *Alkoholprobetrunk*), before the secretagogue effect of histamine was discovered. *In vitro*, alcohol in 1 to 2 per cent concentration has no significant effect on the peptic activity of the gastric juice (Zitovich (7)); when weak alcoholic drinks are taken in conjunction with a meal, the concentration of alcohol in the stomach is probably not greater than this.

The effect on gastric secretion of adding alcohol to a meal was systematically studied in Pavlov's laboratory by Zitovich (7), who used dogs equipped with pouches of the stomach. He found that, when 5 or 10 per cent alcohol was added to a meal of meat, bread or milk, the volume of gastric juice secreted in response to the meal was greatly increased. Alcohol in the same concentration also counteracted the inhibitory effect of fat on the gastric secretion. The secretagogue action of alcohol was especially striking when the first or reflex phase of the secretion was eliminated by introducing the test-meal (in this case, meat) directly into the stomach through a gastric fistula. As Fig. 1 shows, the addition of alcohol restored the course of the secretion to normal and shortened the emptying time of the stomach by one hour. The peptic power of the juice secreted during the first two hours was, however, lower (average, 41 Mett units) than when meat was given with water by mouth (average, 177 Mett units). Zitovich's experiments thus show that, when through loss of appetite the gastric glands fail to give their normal prompt response to the taking of a meal, the ingestion of a beverage of low alcoholic content will help to restore the proper digestion of the food. Nevertheless, the secretion activated by alcohol was not, in these experiments, a perfect substitute for normal reflex secretion, since the enzyme content of the juice was comparatively low.

In the present series of experiments we have been able to show that alcohol, besides stimulating the secretion of fluid and acid by the stomach, may, in certain circumstances, stimulate also the secretion of pepsin. The necessary condition for this additional action is that the alcohol should be relished. It then becomes a positive conditioned stimulus for gastric secretion, increasing the output of pepsin reflexly through activation of the vagal secretory centres.

METHODS

In these experiments we used a dog equipped with a Pavlov pouch of the stomach and a gastric fistula. The experiments were done in the morning, the usual precautions being taken to prevent psychical stimulation of the secretion. 200 c.c. of 5 per cent ethyl alcohol of good quality, warmed to 37° C., was introduced slowly into the stomach through the gastric fistula while the gastric glands were at rest, and the resultant pouch secretion was collected. In control experiments, two other dogs were used, one with a Heidenhain pouch (vagal innervation destroyed) and one with a Bickel pouch (completely denervated) and a gastric fistula. The Bickel-pouch dog could be similarly given alcohol by the gastric fistula; the Heidenhain-pouch dog could be given alcohol by rectum. None of the dogs had ever received alcohol before. The determinations made on the pouch juice were: free and total acidity by titration to Töpfer's reagent and phenolphthalein respectively, and pepsin by Nirenstein and Schiff's (5) modification of Mett's method.

*From the Department of Physiology, McGill University.
Submitted January 14, 1937

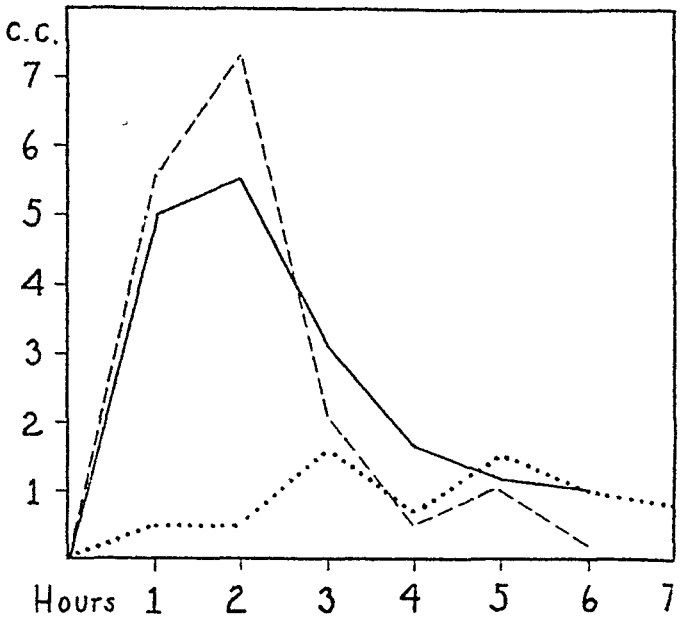


Fig. 1. Volume of juice (Pavlov pouch) secreted in response to the following meals: 100 gm. meat + 100 c.c. water by mouth ——; 100 gm. meat + 100 c.c. water by gastric fistula . ; 100 gm. meat + 100 c.c. 5 per cent alcohol by gastric fistula — —.

RESULTS

The results of the first series of experiments with the Pavlov-pouch dog were uniform. Soon after the dilute alcohol was injected the animal's breath smelled of alcohol and it began to lick its lips. Within 2 or 3 minutes gastric juice began to flow from the pouch. The secretion was brisk for about an hour, and stopped after about 2 hours, when the main stomach was found to be empty. A typical protocol from this series is presented.

Experiment Feb. 4, 1936. Pavlov-pouch dog, female, 14 Kg.

9:05 a.m.	Animal placed on stand. Stomach empty.			
9:05- 9:20	Pouch secretion 0.15 c.c. mucous fluid.			
9:18- 9:20	200 c.c. 5% ethyl alcohol introduced through gastric fistula.			
	Vol. c.c.	Free acidity m.eq./L.	Total acidity m.eq./L.	Pepsin Mett units
9:20- 9:50	3.90	111	120	60
9:50-10:20	2.90	129	138	73
10:20-10:50	0.95	100	109	97
10:50-11:20	0.30			
	8.05 c.c.			

The same experiment was repeated many times on this dog between the end of January and the middle of December, 1936. The course of the "alcohol" secretion, and its total volume and acidity, were always about the same. The volume varied between 7.3 and 9.8 c.c., though latterly it was generally near the upper limits. The concentration of pepsin in the juice, however, underwent a striking change. After the first month or two, during which the experiments were repeated about twice a week, the values for pepsin became gradually higher and higher with each successive injection of alcohol. These results are illustrated graphically in Figure 2. The upper graph shows the volume of juice secreted in eight experiments, selected as typical of different stages during the investigation. The lower graph shows the concentration of pepsin in the juice secreted in these same experiments.

The average value for pepsin concentration increased from 33 Mett units in January to 462 in September—*i.e.*, there was an increase in the digestive power of 1400 per cent. Thus alcohol, which at first did not stimulate the output of pepsin, came in this animal to be a very strong stimulus for the peptic cells.

The other two dogs, whose pouches had no vagal innervation, gave very uniform low values for pepsin (average, less than 50 Mett units) during this whole experimental period.

It was suspected that the explanation of the changed reaction of the Pavlov pouch was that alcohol had become in this animal a positive conditioned stimulus for gastric secretion. There were several reasons for supposing this. During the action of alcohol the dog was clearly slightly intoxicated, and appeared to be in particularly good humor. Although the alcohol was introduced directly into the stomach and the animal was not allowed to smell or taste it, it was soon excreted by the lungs, and the dog could be seen to lick its lips at intervals during the experiment. After the experiments had gone on for some time, it would wag its tail violently, show the greatest pleasure when preparations for the experiment were being made, and follow the movements of the experimenter with much interest. Once or twice a small amount of gastric juice was secreted even before the alcohol was introduced into the stomach. On several occasions the dog was offered 5 per cent alcohol to drink, and took considerable quantities freely. The drinking was followed by a fair secretion of gastric juice of high peptic power. Thus in one of these experiments (Experiment of Oct. 12), when the dog took 175 c.c. of 5 per cent alcohol, the total volume of secretion for two hours was 7.1 c.c. and the average peptic power 271 Mett units. The acidity of the juice was as usual high.

It, therefore, seemed reasonable to conclude that the dog had learned to like alcohol, or perhaps rather the effects of alcohol, and that alcohol had thus become a positive conditioned stimulus for the secretion of pepsin. The actual stimulus would probably be the taste of the alcohol as it was excreted in the breath.

This conclusion is strongly supported by the following experiment, in which the alcohol was given by rectum, instead of through the gastric fistula as usual. The animal had never before received a rectal injection, and objected violently. The digestive power of the juice secreted in response to the alcohol was low, and remained low after a second portion of alcohol had been given through the gastric fistula in the usual way, although the volume of the secretion was nearly normal. In previous and subsequent experiments, in which the alcohol was introduced directly into the stomach under more pleasant circumstances, the diges-

tive power of the juice secreted was very high. The protocol of the above experiment is given below.

Experiment Oct. 14, 1936. Pavlov-pouch dog, female, 14 Kg.

		Vol. c.c.	Total acidity m.eq./L.	Pepsin Mett units
10:00 a.m.	Dog placed on stand.			
10:00-10:30	Pouch secretion 0.5 c.c.			
10:30	Small water enema given to wash out bowel. Dog very excited, struggled, tried to bite.			
10:30-10:50	No secretion.			
10:45-10:50	200 c.c. 5% alcohol by rectum. Same reaction shown by animal. Secretion began in 3 minutes.			
10:50-11:20		2.2	90	122
11:20-11:50		1.7	120	52
11:50-12:20 p.m.		0.7	70	41
		4.6 c.c.		
12:23-12:25	Attempted to give 2nd portion alcohol per rectum. Animal much agitated. Attempt unsuccessful.			
12:25-12:30	200 c.c. 5% alcohol by gastric fistula. Dog did not object.			
12:30- 1:00		3.5	119	59
1:00- 1:30		2.5	144	31
1:30- 2:00		0.9	—	58
		6.9 c.c.		

It is clear that in this experiment the discharge of pepsin was inhibited by the defence reaction of the animal. It is a familiar fact that such emotional reactions frequently inhibit alimentary conditioned reflexes for a considerable period. Since the secretion of pepsin is under the control of the vagus, we can say that the output of pepsin was small owing to inhibition of the vagal secretory centres, although there was still a flow of juice owing to the peripheral action of the alcohol.

Several experiments were performed in which it was attempted, by administration of atropine, to eliminate the vagal participation in the secretory effect of alcohol. The results of these experiments were, however, not very clear-cut. Large doses (0.3 mg. per Kg. of atropine sulfate) entirely abolished the secretion provoked by alcohol, chiefly perhaps by interfering with its absorption, since the stomach contained nearly the original volume of solution after 1½ hours. This is in agreement with the finding of Orbeli (6). Smaller doses of atropine diminished both the volume of the juice and the total output of pepsin, although the evacuation time of the stomach appeared to be not greatly lengthened.

DISCUSSION

Alcohol differs from all other chemical stimulants of gastric secretion in that it acts well from any part of the digestive tract. The composition of the juice secreted in response to alcohol (unless alcohol has become a conditioned alimentary stimulus) is very similar to that of the secretion provoked by histamine, *i.e.*, the acidity is high and the enzyme concentration low. Alcohol, therefore, like histamine, acts chiefly on the parietal cells. The primary secretagogue action of alcohol, like that of histamine, is a peripheral one, since it does not require the integrity of the extrinsic innervation of the pouch. Whether the antagonistic

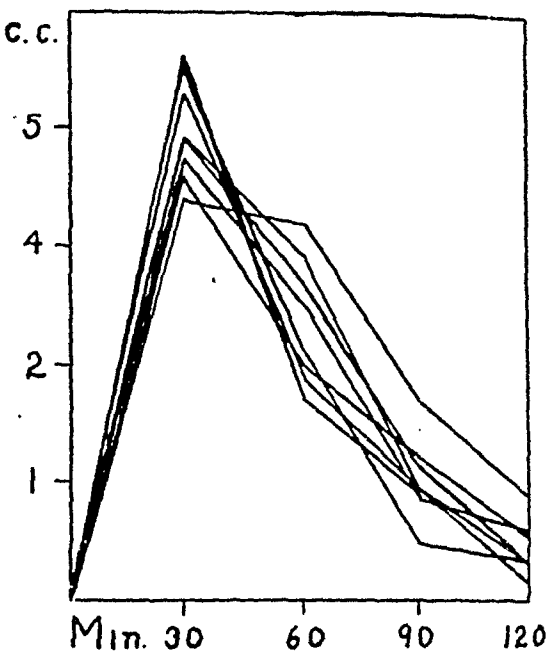


Fig. 2 (a). Volume of juice secreted (Pavlov pouch) after the introduction of 200 c.c. of 5 per cent alcohol into the stomach. 8 experiments.

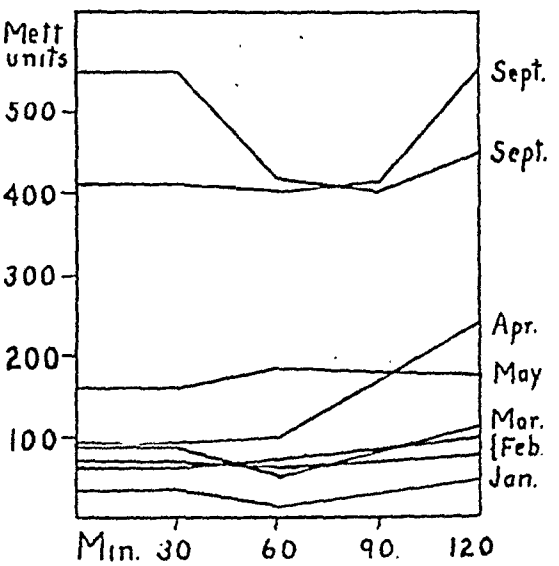


Fig. 2 (b). Concentration of pepsin in the gastric juice in the same 8 experiments.

effect of atropine is due merely to interference with the absorption of alcohol, or whether the intrinsic gastric nerves are involved in the action of alcohol, has not been determined.

From the practical point of view, it is worth while to note that positive alimentary conditioned reflexes may easily be formed with dilute alcoholic beverages. Even in the absence of such reflexes, alcohol through its peripheral action may improve a faulty digestion by increasing the flow of juice. If positive conditioned

from this is that he must recognize such women in time so that he will spare himself the misfortune of being responsible for the misery that will almost certainly follow the removal of all the remaining teeth. A toothless woman, prematurely aged and disfigured, and her long-suffering family will not soon forget to curse the name of any man who brings such misfortune upon them, especially when, as commonly happens, the Heberden's nodes, or the hypertension, or the buzzing in the ears, or the flatulent indigestion, for which relief was sought, continues unchanged.

Fortunately, after one has seen a few of these women, and an occasional man with the same trouble, it is not difficult to recognize the particular human type, and usually when encouraged to do so, they are very willing to keep their remaining teeth. Fortunately there usually are other ways of helping these people besides the one that is now so popular.

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THE ANTI-GIZZARD-EROSION FACTOR

THE apparent discovery (1) of an anti-gizzard-erosion factor may in time prove to be a requisite item for the complete understanding of the etiology and therapy of certain gastro-intestinal diseases. The observed facts may be briefly summarized as follows:

If young chicks are not fed properly they develop a "scurvy-like syndrome," characterized by anemia, hemorrhage, and by crater-like lesions in the lining of the gizzard. The syndrome is prevented by feeding pork liver, lung, kidney, oats and wheat middlings, the meat products being vacuum dried at 50° C. The anti-gizzard-erosion factor which is distinct from the anti-hemorrhagic factor, shows some variation in heat stability and is insoluble in ether and ethyl alcohol. When lung is digested with trypsin, the active principle may be extracted with alkali and precipitated with acid. Thus the active principle appears in the reticulin and not the gelatin fraction of the lung tissue. But when oats are fractionated, the active principle is distributed among three fractions which indicates that the principle is not necessarily related to a protein molecule.

According to Siegfried (2), reticulin is a special substance found not only in the lungs, liver and kidney, but also in the spleen, lymphatic glands and intestinal mucosa. Whether these latter tissues contain the active principle has not been determined, although Bird et al (1) observed slight or no erosions in two chicks fed gastric mucin granules. Chemically the supporting tissues of the body are related to mucin. Thus, it is possible that the growing chicken, requiring much material for the building of supporting tissue, will show gastric mucosal defects, when deprived of this essential factor, much more readily than an adult. It is also possible that the gastric defects are due indirectly to some hepatic disturbance, since the liver plays an important rôle in uronic acid (a building-stone of mucin and chondroproteins) metabolism (3) and since hepatic disturbances are not infrequently associated experimentally with gastro-duodenal ulceration (4). That is, the primary defect resulting from the deficiency of the anti-gizzard-erosion factor may be resident in the liver rather than in the gastric mucosa. The answers to such questions as those suggested and the probable practical worth of such information should stimulate thorough investigation of the chemical nature of the active principle and how its absence in the diet leads to the production of gastric erosions.

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CHEMICAL MEDIATION OF NERVE IMPULSES AND THE GASTRO-INTESTINAL TRACT

THE Nobel prize in medicine for 1936 was awarded to Loewi and Dale for their work in developing the theory of chemical mediation of nervous effects. The theory maintains that the arrival of an impulse at the nerve ending liberates a chemical substance, which acts upon the receptive mechanism of the cell to produce excitation or inhibition, and that the same type of mechanism transmits the impulse across synaptic connections in autonomic ganglia. It should be of timely interest to call attention to the application of this relatively recent concept to gastro-intestinal problems.

Stimulation of the vagus nerve has been shown to liberate acetylcholine from the nerve endings in the stomach (1) and in the small intestine (2). It has also been shown that an adrenaline-like substance (sympathin) is liberated in the intestine and liver by the stimulation of their sympathetic innervation. Future work will in all probability confirm the generalization that sympathetic fibres to the gastro-intestinal tract liberate sympathin and that parasympathetic fibres liberate acetylcholine. However, important exceptions have been noted to this general principle in so far as the anatomic classification of the autonomic nervous system is concerned. For example, anatomically the sweat glands are said to be innervated by the sympathetics; yet these nerves liberate acetylcholine (4). The blood vessels are said to be sympathetically innervated; yet certain of the nerves passing to the blood vessels liberate both sympathin (adrenergic fibres) and acetylcholine (cholinergic fibres) (5). Were a similar situation to obtain in regard to the autonomic innervation of the intestinal musculature, an explanation might be provided for certain inconsistencies encountered in this field. For example, electrical stimulation of the parasympathetic (vagus) and sympathetic (splanchnic) nerves of the gastric musculature may result in either excitation or inhibition. Or, under more physiological conditions, the vagus nerves may produce either gastric motor inhibition, as when HCl is introduced into the duodenum (6), or gastric motor augmentation, as when hypoglycemia (acting centrally) is produced by insulin (7). It is conceivable that the body accomplishes these divergent results over the same nerve trunk by the selective utilization of adrenergic fibres in the first instance and cholinergic fibres in the second; in

sion disappears from the circulating blood in approximately 2-3½ hours. It was observed that the size of the fat globules did not exceed that of chylomicrons, assuring safety of the injections, as far as fat embolism is concerned.

To demonstrate the utilization of fat, if any, the following plan was conceived. Three puppies of the same litter, each weighing 6 lbs. (2.274 kg.) and measuring 18 in. (46 cm.) from nose to root of tail, were used. The surface area of each puppy has been computed to be .190 sq. m. according to the method of Cowgill and Drabkin. Taking the basal heat production at 790 cal. per sq. m. per day, makes the total basal metabolism of such a puppy 150 cal. per day.

One puppy, serving as a control, was placed on a diet consisting of fresh ground beef heart. The amount given daily was calculated to be equivalent to the number of calories required. Adjustments of the amount of food were made every few days according to the physiological increase of weight.

The second puppy was placed on a semi-starvation diet, viz. it was given 75% of the calculated requirement of calories in form of the same diet which was given the first puppy.

The third puppy was getting the same amount of food as the second and the deficit was covered with a corresponding amount of fat emulsion.

The first week subcutaneous injections were given daily. They were painful and had to be discontinued because the fat was apparently very slowly or not at all absorbed. After a few injections, made each time at a different place, the entire skin of the trunk became uniformly indurated as in elephantiasis, and seemed to be firmly attached to the deeper tissues, simulating an armor. The subsequent injections were given intraperitoneally. The semi-starving puppy died 32 days after the beginning of the experiment.

The puppy receiving fat injections survived. It did not have the appearance of a healthy animal; it had a poor appetite and was shy and not so lively and playful as the control puppy. Although it was gaining weight, the increase was less pronounced that in the control animal. It was sacrificed three months after the start of the experiment. The autopsy revealed an extensive aseptic peritonitis. There was a small amount of a slightly hemorrhagic serous exudate and numerous adhesions between the intestinal coils. Considerable fat deposits were found in the subcutaneous tissues. The histologic examination disclosed an abnormally high fat content of the lungs and heart muscle while the spleen, liver, brains, omentum, mesenteric lymph glands and retrobulbar tissue of the orbits had a normal aspect. It was surprising to find such extensive pathologic processes in the peritoneal cavity as the animal, although apparently not healthy, remained alive for three months and did not seem to be losing ground until it was sacrificed. The experiment was repeated on another puppy with identical results: intraperitoneal injections caused an aseptic peritonitis.

This experiment showed that 1. subcutaneous injections of fat emulsion are not feasible; 2. intraperitoneal injections cause an aseptic peritonitis; 3. fat emulsion is apparently absorbed from the peritoneal cavity; 4. fat injected intraperitoneally sustains the life of a semi-starving dog.

In view of the pathologic lesions following intraperitoneal injections, this mode of introduction of fat emulsion could not be considered for therapeutic purposes. The veins in small puppies are too small to allow daily intravenous injections, particularly because a heavy gauge needle must be used. Therefore another experiment was planned. Two adult dogs were used, one weighing 11.25 and the other 10.8 kg.; the first, serving as a control, was completely starved; only water was offered. The other was also completely starved, but in addition to water, daily intravenous injections of 60 c.c. of the fat emulsion were administered. Several times the fat was injected into the femoral artery. All the injections were well tolerated. They were apparently not painful and no thrombi were noted.

TABLE II

Days of starvation	Weight of Control Animal	Weight of dog receiving fat injections
1	11.25 kg.	10.80 kg.
6	10.90	9.90
9	10.60	9.40
12	10.10	9.00
16	9.20	8.55
19	8.70	8.30
22	8.40	8.10
27	7.90	7.60
28	7.70	7.60
31	6.52	6.75
32	6.30	6.55
34	6.15	6.50
36	6.00	6.45

A paradoxical phenomenon was observed the first two weeks: the animal receiving the injections lost weight more rapidly than the control dog, as can be seen from Table II. The amount of water consumed by each animal was approximately the same so that the difference could not be explained on this basis. We can offer no explanation for this observation. However, after the first 16 days the average loss of weight of the dog receiving injections was smaller than that of the control animal. As can be seen from the accompanying table, the control dog lost 3 kg. between the 6th and 27th starvation days and the other only 2.3 kg.

Between the 6th and the 36th day the losses were 4.90 and 3.55 kg. respectively. The control dog died on the 36th day of starvation. Injections were continued in the other dog for ten days more, during which the animal lost 0.45 kg. This dog weighed at the start of the experiment 0.45 kg. less than the other; in spite of this it survived the control. Throughout the whole experiment the dog receiving the injections was more vigorous and lively than the control. A period of ten days was deemed to be sufficiently long to eliminate the possibility of a merely accidental survival.

To corroborate the findings, the whole experiment was repeated on another pair of dogs, one weighing 10.9 and the other 10.2 kg. The latter was given intravenous injections of the emulsion daily. The control animal died on the 31st day of starvation, while the other dog lived on; injections were continued for

additional two weeks before the experiment terminated. During the starvation period this dog lost 4.2 kg. and the control 4.6 kg.

It is evident that the quantity of fat administered in these experiments was able to consistently prolong the life of otherwise starving animals and to reduce the eventual weight loss. As an emergency measure it seems that parenteral administration of fat emulsion might have sufficient virtue for clinical trial. Danger from fat embolism is virtually non-existant and all lines of evidence point clearly to the fact that intravenously administered emulsions are utilized.

SUMMARY

1. By employing the process of homogenization it is possible to prepare a stable sterile fat emulsion which, if administered parenterally, produces no fat embolism.

2. Subcutaneous route is not recommended because the injections are painful and the emulsion is absorbed very slowly.

3. Intraperitoneal route is not available because the fat emulsion causes an aseptic peritonitis with resulting adhesions.

4. Intravenous infusions are well tolerated by dogs.

5. Intravenous infusions prolong the life of semi-starving and completely starving dogs.

6. The fact that a completely starving dog receiving daily injections of a fat emulsion survives the starving control, serves as a definite proof of utilization of the introduced fat.

7. Although results of animals experimentation can be applied to human pathology only with a great caution, the results of the above described observations prove that an intravenously administered emulsion of fat is available for metabolic purposes.

The author makes grateful acknowledgement to Dr. M. B. Visscher, Head of the Department of Physiology, for his invaluable suggestions.

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Pruritus Ani: A Preliminary Report of One Hundred and Thirty-Three Cases Using Triple Distilled Water*†

By

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PRURITUS ani is as fascinating as is its treatment, at times, discouraging; for this reason any form of therapy carrying with it a surprising percentage of temporary and permanent cures is worthy of consideration.

In this presentation, it is not our purpose to recommend the use of distilled water as a routine procedure, but rather to present our results following the use of injections of triple distilled water. Credit is given Hanes (3) for first employing this treatment in pruritus ani, although Davis (2) has since used it extensively with most gratifying results. The latter believes that the tissue changes are chemical, and not bacterial, and that the introduction of double distilled water dilutes the chemicals, aids in their absorption and in the excretion of those which he thinks tend to accumulate in the anal and perianal skin and induce pruritus. Tashian (5), on the other hand, believes that triple distilled water stimulates the defense cells of the reticuloendothelial or histiocytic system.

METHOD

The method we employ (4), which is a modification of that primarily suggested, is as follows: The patient is placed in an exaggerated left lateral position. The quadrant causing the most distress, or the one appearing most inflamed, is selected for the first injection. The area is swabbed briskly with alcohol or tincture of green soap and is dried with sterile gauze. A point just beyond the periphery of the pruritic zone is selected and touched with tincture of iodine. This is wiped off with alcohol, and when the skin has dried an intradermal wheal is made with one per cent novocain, using a small hypodermic needle. A 21 gauge needle, two and a half inches in length, to which is attached a syringe containing one c.c. of novocain, one per cent, is slowly advanced beneath the pruritic skin. At this point the novocain is deposited. The needle is held in situ and a 10 c.c. syringe containing 10 c.c. of triple distilled water substituted. The contents are slowly injected until the entire amount is used. Should pain or discomfort attend its introduction, injection is suspended for a few seconds. Each quadrant is similarly treated at intervals of three or four days, until a series of eight injections has been given, or until the patient is symptom free. In over 50 per cent of our cases, only five c.c. were employed, instead of the usual quantity.

RESULTS

Over a four-year period ending with 1933, 133 cases were treated in the clinics of the Temple University and Graduate Hospitals and in private practice (1). In this group there were 85 males and 48 females, with an average of 41 years. The duration of symptoms

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ranged from nine months to 23 years. Of the 133 patients, 91 had had one or more operations on the anorectum without relief.

A study of the charts for these cases reveals that the average number of injections administered was nine, the extremes being three and 23, as shown by the following table:

4	patients	received	3	injections
4	"	"	4	"
18	"	"	6	"
41	"	"	8	"
38	"	"	10	"
11	"	"	12	"
2	"	"	13	"
8	"	"	14	"
4	"	"	16	"
1	"	"	18	"
1	"	"	20	"
1	"	"	23	"

In three cases treatment was interrupted because of the development of ischiorectal abscess. This occurred when this form of therapy was first begun, and we felt it was the result of improper cleansing. Since iodizing the skin prior to making the injection has been instigated, no concurrent infection has been observed. Of the remaining 130 patients, 42 did not return for a check-up, or did not reply to our questionnaire. Thirty-nine of these 42, however, were symptom free at the time of their discharge from clinic. The reports on 88 cases, representing a lapse of between two and a half and three years, are as follows:

Symptom free (cured)	27 or	30.7%
Improved	56 or	63.6%
No Relief	4 or	4.6%
Worse	1 or	1.1%
	88	100.0%

CONCLUSIONS

A preliminary report of 133 cases treated with triple distilled water is offered. Following a period of 30 to 36 months, 94.3 per cent of the above cases were benefited. Of these, some were completely symptom free, and some were improved.

In those cases where the associated pathology has been removed or corrected without effect, or in which the etiology is involved, we feel that this form of therapy is worthy of a definite place in our armamentarium for the correction of pruritus ani. Its results to date certainly justify any further study that may be needed to develop the plenitude of its possibilities.

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Renocolic Fistula*

Report of an Instance Roentgenologically Simulating Carcinoma of the Colon

By

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RENOCOLIC fistula is an extremely rare complication of renal disease. Its occurrence has been known for many centuries. A review of the literature reveals very few references regarding this condition. Hippocrates mentioned a case of rupture of a renal abscess into the intestines. Since then but few single case reports have been recorded. The most complete early study of renal fistulae was made by Rayer (1), who cited a number of authors reporting cases on this subject. Mertz (2), in 1931, summarized all reported cases in the literature and recorded two of his own. Vermooten and McKeown (3) more recently reviewed the literature, added another case. The intimate relationship between the colon and the kidneys is an important factor in the formation of fistulous communications between these two organs.

Renocolic fistula are more commonly located on the right side, which is no doubt due to the closer relationship of the right kidney and colon than that on the left side. The majority of cases reported in the literature were found to involve the right kidney. However, a few cases have been reported occurring on the left side. D'Allaines and Roufliac (4) report a case of a fistula between the left kidney and colon; and Roman (5) recently reported another case of a fistula between the left kidney and the colon with external fistulization, with extensive tuberculosis of the kidney.

The primary etiology in most instances is due to a pyelonephritis, producing a secondary perirenal inflammation, suppuration with subsequent necrosis and abscess formation and finally perforation into the colon. Of 20 cases collected from the literature by Vermooten and McKeown (3) 8 were associated with renal calculi, 2 with tuberculosis, while 13 or 50% of the cases were described as having a pyelonephrosis.

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Fig. 1. A large massive irregular filling defect is shown at A, involving the ascending colon, presenting all the characteristic roentgen signs of a carcinomatous growth. Note the irregular fistulous tract at B leading towards the spinal column.

In 12 cases, an acute or chronic suppurative perinephritis was observed.

It is of interest to emphasize that in the majority of cases the original source of infection occurred in the kidney. In reviewing the literature of collected series of cases it must be pointed out that in not a single instance was the primary lesion observed in the bowel.

In the diagnosis of renocolic fistula, the X-ray affords one of the most valuable measures in determining the exact nature of this complication. Before the advent of roentgenography, the diagnosis of renocolic fistula was never made clinically. It was then made either at autopsy or by surgical procedures. In recent years, however, a few cases of this complication have been reported which were diagnosed by means of the X-ray. The fistulous communication had been encountered by pyelographic studies of the kidneys. In Blanco (6), Barnes (7), and Vermooten and McKeown's cases, the roentgen examination of the genitourinary tract revealed evidence of this complication. In reviewing the available recent literature, the roentgen diagnosis in most instances had been made by means of the routine retrograde pyelographic studies. In no instance was a case recorded in which the diagnosis was made by a barium enema examination, with the exception of Riaboff's (8) case, in which the roentgenogram revealed a filling defect in the first portion of the transverse colon.

In this presentation, a second case of renocolic fistula is recorded in which the barium enema gave the first clue as to the true nature of the condition. The barium enema revealed a large irregular filling defect in the ascending colon, presenting all the characteristic roentgen signs of a malignant growth with

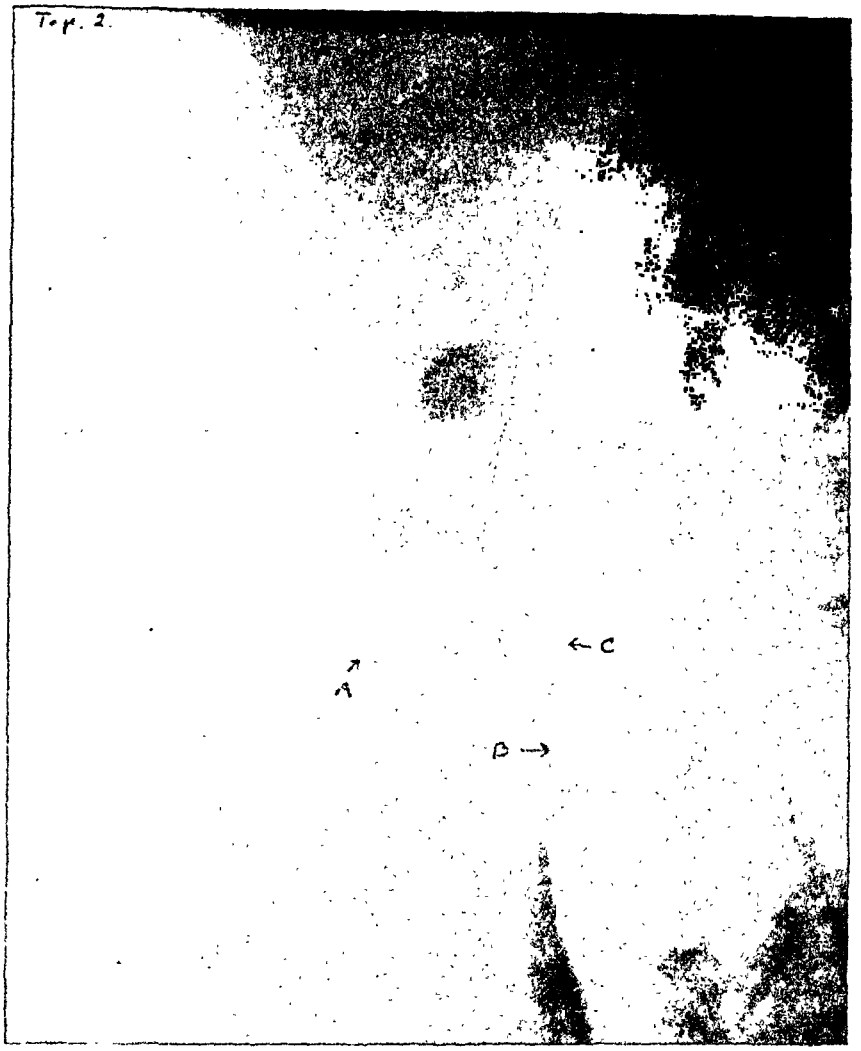


Fig. 2. Retrograde pyelogram illustrates the poor filling of the kidney pelvis and faint outline of the inferior calyx at A. The superior calyx is dilated and blunted. Note the pressure defect upon the upper ureter at B produced by the mass. A ureteral kink is shown at C.

a large mass on the right side. On close observation, an irregular narrow channel could be seen leading from the colon toward the mass which suggested a fistulous tract. A pyelographic study was also made in this case, which presented evidence of a pyelonephritis. The fistulous tract is not visualized on the pyelogram, which indicated that the communication existed between the colon and perinephritic abscess. At operation a large retroperitoneal inflammatory tumor was found with multiple perinephritic abscesses of the right kidney. A fistulous communication was observed between the kidney mass and the ascending colon.

SUMMARY

A case of renocolic fistula is reported, presenting all the roentgenographic signs of carcinoma of the ascending colon. This is the second case to be recorded as far as could be ascertained from the literature in which a barium enema method of examination revealed roentgen evidence of extensive colon involvement with a fistulous tract leading into an inflammatory mass on the right side. The roentgen ray offers the only means of establishing a preoperative diagnosis.

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A Study of the Cardia*

By

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and

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AN increasing clinical interest in dysphagia and obstructions at the cardia has stimulated a renewal of efforts to study the sphincter under normal and well controlled experimental conditions. The term "cardiospasm" has been used to indicate all types of obstructions until relatively recently. The work of Hurst and Rake (1) aroused new interest in this clinical condition by showing that a failure of the relaxing mechanism (*achalasia*) alone could constitute an obstruction to the passage of food. Their conclusions were made after studying post-mortem material from patients who had suffered from functional obstruction at the cardia. There was no hypertrophy of the sphincter but a degeneration of Auerbach's cells seemed to have taken place.

Because of the mechanical difficulty of keeping a balloon in the cardia, registration of its activity for any continuous period has met with failure. The balloon either rises into the esophagus or slips into the stomach. Carlson, Boyd and Pearcy (2) used a rubber plug placed on the stomach side of the cardia, and attached the cardia balloon so that tension could be placed on the plug, thus holding it snugly to the lower surface and maintaining the balloon in the cardia and lower esophagus. While this apparatus could be used on the anesthetized animal to study tonus changes and the effect of nerve section and stimulation, it was used in only one animal with a permanent gastrostomy and esophageal fistula. For a comprehensive survey of the literature on the innervation of the esophagus, cardia and stomach, together with the effects of nerve section, the reader is referred to the work of McCrea (3).

PROCEDURE

Dogs with gastric and esophageal fistulae were used. They were trained to lie quietly without restraint on a table made comfortable by a pad. All animals were healthy and in good physical condition; no anesthesia was used in making any of the observations here reported.

Esophageal fistulae were made about one inch below the level of the cricoid cartilage. Under aseptic technique a mid-line incision was made in the neck, the ribbon muscles were separated from the deep tissues and the esophagus pulled up to the left of the trachea. Care was taken to prevent injury to the recurrent laryngeal nerve. The walls of the esophagus were then sutured separately to the fascia overlying the ribbon muscles and to the skin before making the ostium. No special postoperative care was necessary, and the animals were able to swallow liquids and solids with a minimum of leakage from the fistula.

The gastric fistulae were made at a separate operation under ether anesthesia. The abdomen was opened by a right rectus incision. A segment of jejunum or ileum about 7 or 8 cm. long with a suitable blood supply was resected. The distal end was anastomosed to an opening made in the anterior wall of the fundus of the stomach. The proximal end was brought to the surface through the original incision and sutured to the peritoneum, muscle and skin in separate layers. The continuity of the gut was restored by a closed, end-to-end anastomosis as described by Martzloff and Burget (4), and the abdomen closed. This type of fistula has been found to have distinct advantages over the usual gastrostomy. Since direction of peristalsis is from outside inward, any material which is forced into the segment of the gut as a result of increased intragastric pressure is swept back into the stomach. No leakage of gastric juice from the fistula occurs, and therefore no care is necessitated.

For recording activity of the cardia, a thin layer of sponge rubber was wrapped about the perforated end of a rather rigid tube and covered by a delicate balloon. The tube extended through the length of the balloon, which was 3 cm. long and 1 cm. in diameter. This was placed in the cardia through the esophageal fistula. The cardia can easily be felt and the balloon held in place throughout the experiment. This balloon was never distended with air. It is soft and easily compressed with the sponge rubber holding sufficient air for recording any change in the tonus of the cardia when attached to a sensitive tambour. This balloon produced no discomfort when in place and was so flexible as to permit a record of slight changes of tonus in the sphincter. In early experiments a second balloon of thin rubber attached to a very small tube was placed in the esophagus well above the cardia. This balloon was attached to a tambour by way of a T-tube. When the operator desired to stimulate the esophagus, he had only to blow in the arm of the T-tube, distend the small balloon, and initiate a peristaltic wave. The stimulus was recorded by the tambour. Later it was found desirable to use this balloon without the T-tube to record peristalsis of the lower esophagus and use a third balloon above this one, unattached to a tambour and used solely for stimulating purposes. At the time of blowing into the balloon, the operator recorded the stimulus by a key and signal magnet. While this set-up might seem unphysiological, the tubes were small and did not irritate the esophagus to the extent of producing reflex contractions, nor were there any signs of discomfort displayed by the animal. A larger balloon was placed in the stomach by way of the gastric fistula and connected with a chloroform manometer for recording activity of the fundus and body. This balloon was distended with air sufficiently to record pressure changes but not enough to elicit contractions.

Observations usually were made ten to fifteen hours after feeding but in some instances earlier records were taken. All animals had gastric and esophageal fistulae as described. Records were made under the following additional conditions: normal; one vagus sectioned in cervical region; both vagi sectioned in cervical region; double vagotomy in the thorax; double vagotomy in the thorax with one vagus sectioned in the cervical region; both vagi and both splanchnics sectioned in the thorax; sympathetics sectioned as fibers approached the cardia by way of the

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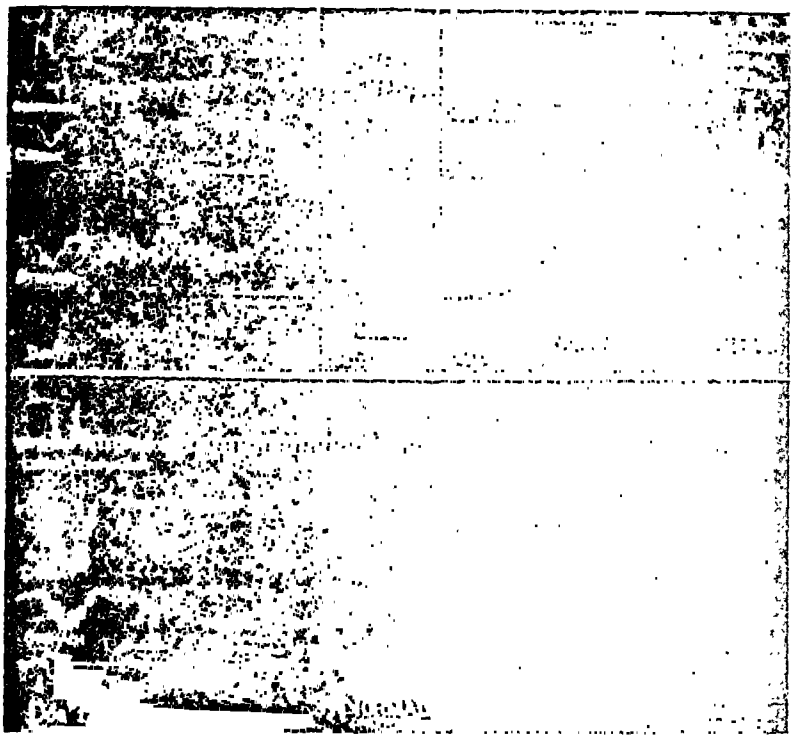


Fig. 1. Tracings before nerve section. That taken from dog 7 shows the cardia relaxation and the lower esophageal activity when the cardia balloon was drawn to this position. The effect of swallowing is shown (dog 13). In tracing from dog 3 the effect of continuous activity of the esophagus on cardia and stomach is made clear. The lower half of this figure (dog 17) shows remarkable relaxation. Here a balloon recorded activity of the lower esophagus also. A light stimulation and even a swallow did not produce a wave that traveled down to the cardia, or if it did, it was so weak as to not record.

left gastric artery; sympathetic section together with double vagotomy in the thorax.

RESULTS

Findings on the Normal Animal: When the balloon is lowered into the cardia by way of the esophageal fistula, the operator can definitely feel when the cardia is passed. On pulling back from the stomach into the lower esophagus, a resistance is felt which is suddenly released as the balloon passes through the cardiac sphincter. The observations of Carlson and Luckhardt (5) were confirmed in that the tonus of the cardia is usually increased with hunger contractions of the stomach. Following an act of deglutition, the cardia and stomach are seen to begin relaxation while the peristaltic wave is still high in the esophagus. The height of relaxation is reached as the wave approaches the cardia. Following this relaxation, there is usually a temporary rise in tonus of the sphincter. Exactly comparable results are seen following inflation of the balloon in the upper part of the esophagus. If a series of secondary peristaltic waves were elicited by the distended balloon, a marked fall in tonus of the cardia is maintained throughout the esophageal activity (Fig. 1).

An interesting observation was made in one instance where the cardiac balloon had been pulled into the lower esophagus; the stomach was seen to relax in response to a peristaltic wave in the upper esophagus, but this wave was not picked up by the cardiac balloon. It was this observation that led us to place an extra balloon in the esophageal fistula to record the activity in the lower esophagus. By this means a check could be made upon the ultimate termination of the wave initiated in the upper esophagus. With very weak distention of the esophageal balloon a wave may be elicited and start to pass down the esophagus. The cardia and stomach relax, but no evidence of the wave having reached the lower esophagus can be obtained. With stronger distention of the upper balloon, the wave traverses the length of the esophagus and is definitely recorded by the lower esophageal balloon with the cardia and stomach relaxed as before (Fig. 1). That this relaxation in the cardia is absolutely independent of diaphragmatic activity is seen in Fig. 3, which was taken on a hot day when the dog was panting. The respiratory movements are recorded by the balloon in the lower esophagus.

Effects of Vagus Section in the Neck: Unilateral section of the vagus in the neck was carried out on six dogs. In three the left vagus was cut; and in three the right. Tracings were taken as early as four hours after the operation (Fig. 2). During the first twenty-four hours the esophagus is partially paralyzed and somewhat atonic. Although relaxation of the cardia can be elicited upon distention of the esophagus, the pressure necessary is greater than that re-

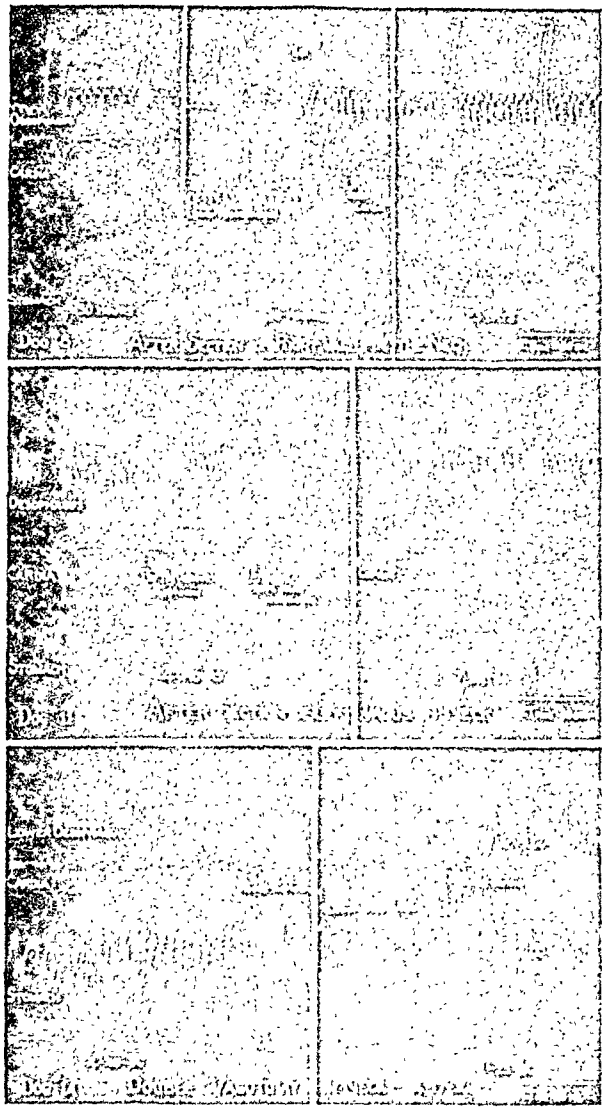


Fig. 2. In tracing for dog 8 following section of right vagus in neck, a normal response is given. Dog 11, no effect from section of left vagus in neck. Section of both vagi (dog 14) results in paralysis, tracing showing respiratory curves.

quired in the normal animal, and the relaxation of the cardia is not as marked. The tonus is regained within a few days, and relaxation follows swallowing or distention of the esophagus, apparently as well as before the nerve section. The threshold, however, remains a little higher than in the normal animal. The type of response and relative time relations are little if at all altered. There seemed to be no difference in the effect produced with regard to section of right or left vagus.

Section of both vagi in the neck was performed on three dogs, resulting in complete paralysis of the esophagus. Under this circumstance it is impossible to initiate a wave in the esophagus. The cardiac balloon, when pushed through the cardia into the stomach, could be returned to the esophagus with less resistance than was present before the operation. In the course of a few days the cardia regains some of its tone, but never was it possible to elicit relaxation by distending the esophageal balloon. These dogs, of course, are difficult to maintain since they aspirate food into the lungs and die of pneumonia. One of our dogs lived fifteen days. All showed hypertonic stomachs in the course of a few days. This was especially noticeable when it was attempted to feed them by way of the gastric fistula, food would often be forced either back through the gastric fistula or into the esophagus. This hypertonicity seen in the stomach did not appear to be present, at least in high degree, in the cardia. Hunger may have been a factor.

Effects of Sectioning the Vagi in the Thorax: There were nine dogs in this group, five of which had the vagi sectioned immediately (2-3 cm.) above the diaphragm and four higher at the lung roots (6 to 8 cm. above diaphragm). The approach was made through the left side, posteriorly, between the eighth and ninth ribs. An incision was made about 6 cm. long parallel with the ribs. After entering the thoracic cavity, a small spreader was used to hold the ribs apart. The lung fell away and revealed both vagi—the left one anterior and right one posterior to the esophagus with the branch from the left coming down to join the right one about one inch above the diaphragm. Both vagi and the connecting branch were grasped with hemostats and sections of nerve removed by cutting on either side of the clamps. The thorax was then quickly closed and the dogs all made an uneventful recovery. Tracings were taken twenty-four hours after the operation and at intervals for six months. In both high section (dog 11) and sectioning immediately above the diaphragm (dog 1) the relaxation mechanism in the cardia and stomach was unaffected. There was no evidence of spasm or paralysis in any of these animals. It is impossible to detect any difference in the type of relaxation or time relations as compared with the normal dog either immediately or several months after operation (Fig. 3). (Dog 11 had vagi cut low at first, then resectioned high in thorax eleven months later). These animals also showed a relaxation of the cardia and stomach when a weak stimulus was applied to the upper esophagus without showing a peristaltic wave in the lower portion. Stronger distention produced a wave which was recorded by the lower esophageal balloon with the usual relaxation of the cardia and stomach.

Vagi Sectioned in the Thorax with One Cut in the Neck: Three animals thus operated upon showed no apparent change in the type of activity in the cardia and stomach following peristalsis in the esophagus. They did show, however, a lowered irritability as was seen in animals with only one vagus sectioned in the cervical region (Fig. 4).

Effects of Section of Sympathetics: The sympathetic supply to the cardia, as described by Knight and Adamson (6), was sectioned in two dogs. Through a left rectus incision the left gastric artery was exposed high up on the lesser curvature of the stomach. It was freed and ligated along with its vein. The esophageal branch of the artery was dissected free, along with a bundle of nerve tissue lying along side, and

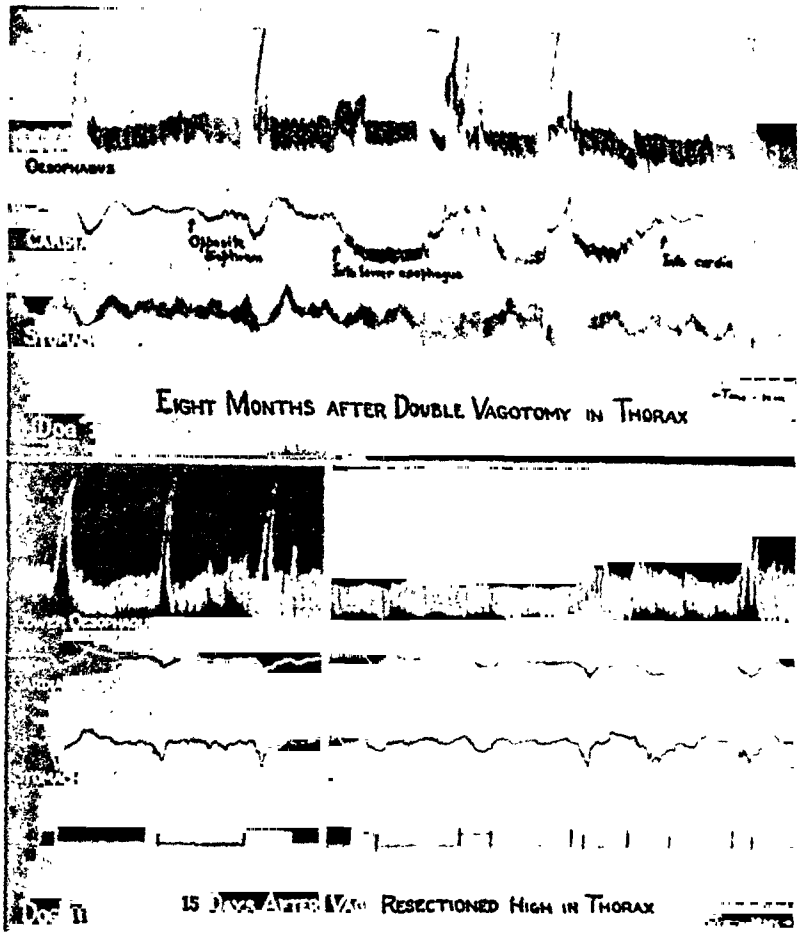


Fig. 3. Upper tracing vagi cut above diaphragm with an active cardia. Lower tracing shows effect when nerves were sectioned as high in the thorax as possible —good relaxation of cardia and stomach. Here a balloon in the lower esophagus caught the wave on strong stimulation but on light stimulation there is no indication of a wave in the lower esophagus. Respirations were rapid and completely without effect upon the cardia relaxation.

pulled over to the dog's right. The deep aspect of the left gastric artery was thus exposed and many strands of nerve tissue were found passing from the coeliac ganglion to the lower end of the esophagus. These were all divided at their peripheral ends. The section was carried centrally until the left side of the coeliac axis was exposed. The left gastric was then ligated at its origin and the segment removed along with the mass of nerve tissue that had been dissected free. This operation was followed by no immediate or late spasm or paralysis of the cardia, nor was the tone of the cardiac sphincter appreciably altered. Again the cardia and stomach showed relaxation when the upper esophageal balloon was distended whether or not a wave of the esophagus was picked up by the lower esophageal balloon (Fig. 5). Likewise two dogs with the splanchnic nerves cut in the thorax continued to give normal cardiac relaxation.

Effects of Sectioning Both Vagi and Sympathetics: Three dogs were prepared with a combination of operations—two with double vagotomy in the thorax and sympathectomy in the abdomen as above described, and one with double vagotomy in the thorax together with splanchnicectomy. In these animals gastric motility was reduced but returned to normal in the course of a few weeks. The cardia and stomach continued to relax following initiation of a wave in the esophagus. While the relaxation of the cardia seemed complete, probably relaxation of the stomach was less than normal. The nature and time relations of the relaxation were unaltered so far as could be determined (Figs. 6 and 7).

In one dog the esophagus was cut across and both ends brought to the skin in the neck. A stimulating balloon could be used in the upper segment while a recording balloon was in the lower esophagus and one in the cardia. Stimulation in the upper segment brought about the usual esophageal wave and relaxation of the cardia. The vagi were now cut high in the thorax of this dog, and twenty-four hours later a test

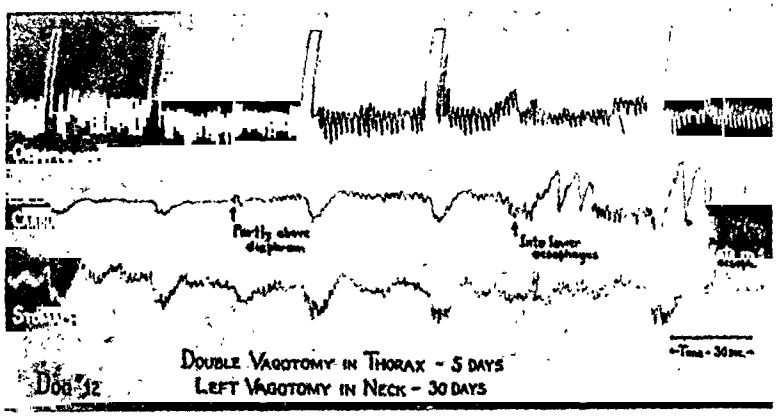


Fig. 4. Cervical section of one vagus following double vagotomy in the thorax leaves an apparently normal reflex.

showed both a wave in the esophagus and relaxation of the cardia. Swallowing produced the same effect. Even upon a light stimulus to the upper segment relaxation of the cardia took place without an apparent wave in the lower esophagus. This observation indicates the sensitivity of the inhibitory reflex in the cardia and implies the presence of long vagus fibers along the esophageal wall that are not reached in sectioning the trunks of the nerves, or an intrinsic mechanism that is dependent upon an outward flow of central impulses over the vagi.

In an attempt to destroy any long vagus fibers leaving the trunk in the thorax, the nerve trunks were freed from the esophagus over an area from the diaphragm to the lung roots without being sectioned. Following recovery from this operation, the dog showed normal relaxation of the cardia and stomach.

This mechanism is not paralyzed by atrophine. Dogs were given as high as 3 mg. atropine sulphate without affecting the inhibitory reflex of the cardia. However, the stomach response was materially reduced or abolished by this dosage.

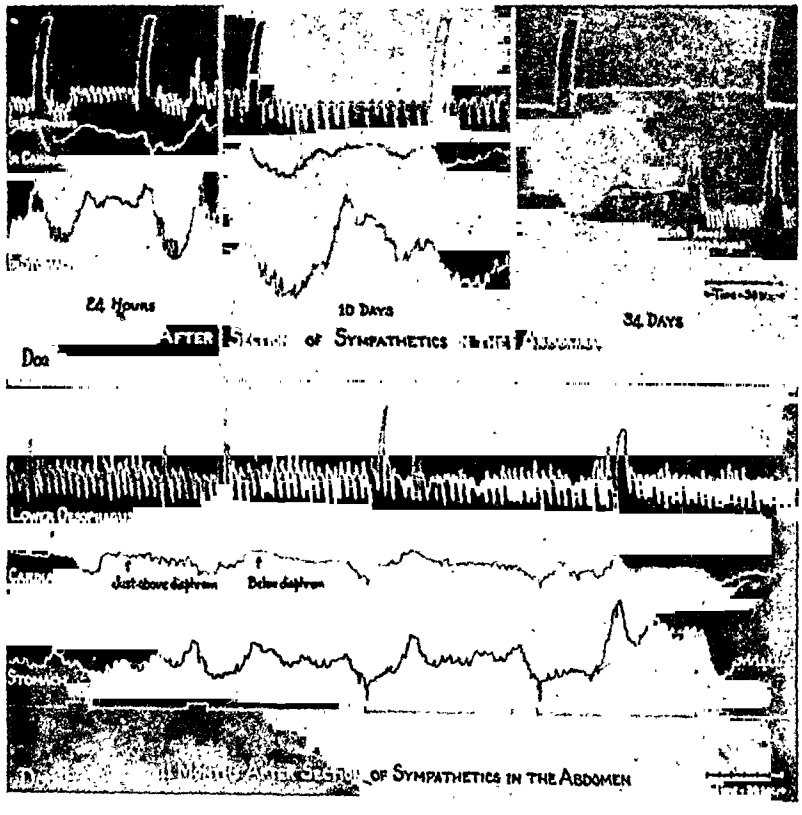


Fig. 5. Tracing from dog 7, 24 hours, 10 days, 34 days, and 11 months after section of the sympathetic fibers to the cardia as described by Knight. The relaxation reflex is still present.

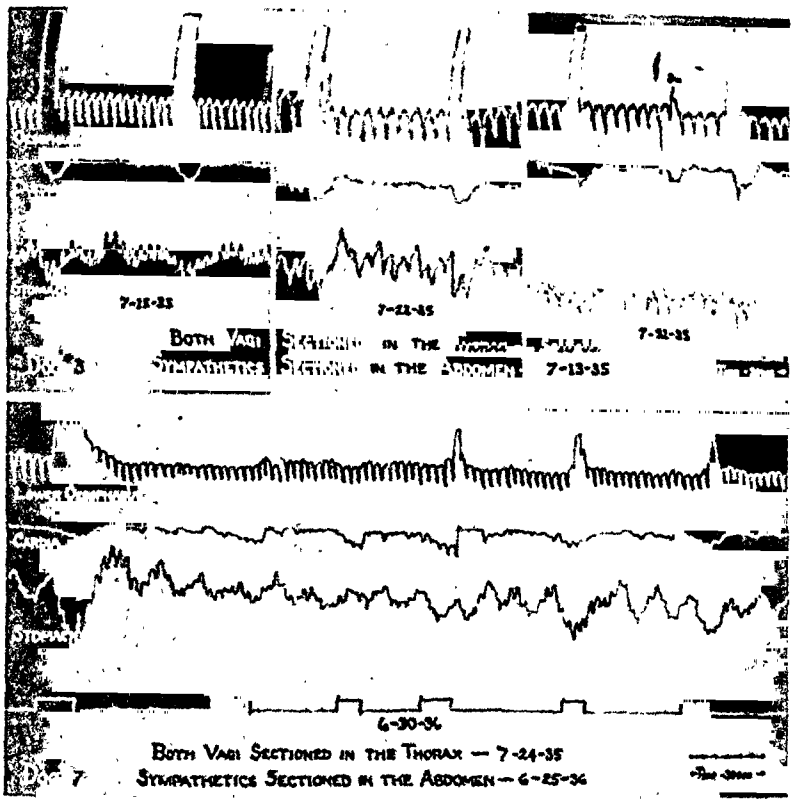


Fig. 6. Tracings following section of the vagi in the thorax together with sympathetic section in abdomen. There can be no doubt that the mechanism which brings about this reflex inhibition is still present.

Further investigation of this problem is being made by way of a histological examination of the esophagus for long nerve fibers and the possibility of a myenteric plexus. While studying the tonus of the esophagus and cardia in connection with hunger contractions, Carlson and Luckhardt (5) expressed the opinion that the dog's esophagus did not possess a myenteric plexus. If this is confirmed, the necessary impulses must be carried by way of long vagus fibers in the viscus. This, of course, would bring up the question as to the extent vagus impulses have been cut off in all of those experiments by physiologists where the activity of these nerves was supposed to have been removed by sectioning the trunks above or below the diaphragm.

DISCUSSION

Our observations as regards paralysis of the esophagus following vagus section in the neck confirm those of Kronecker and Meltzer (7) working on rabbits, but we failed to see a marked cardiospasm in the dog. Cannon (8) found that section of the vagi in the neck in cats leads to an increased tonus of the cardia lasting several days. The smooth muscles at the lower portion of the esophagus in these animals was ineffective in forcing food through the cardia. Kelly (9) cut the vagi in the cervical region in cats and noted a retention of food in the esophagus by means of the fluoroscope. He felt the increased tonus of the cardia prevented passage of the food. Knight has recently reinvestigated the innervation of the esophagus and cardiac sphincter in an attempt to obtain a rational basis for the surgical treatment of achalasia. Upon sectioning the vagi in the cat, Knight (10) obtained a partial obstruction at the cardia which was maintained, resulting in a greatly dilated esophagus. He found that if the sympathetic fibers were sectioned, this obstruction did not occur or if present, was removed. He attributed this effect of vagus section to a failure of the sphincter to relax under the peristaltic wave of the esophagus.

In 1883 Kronecker and Meltzer (7) noted relaxation in the cardia following repeated acts of deglutition. They assumed this to be a central inhibition of vagus motor tone to the cardia. A similar phenomenon was observed by Langley (11) in rabbits. Cannon and Lieb (12), while working on cats, made the observation of a receptive relaxation in the cardiac portion of the stomach. They noted that the stomach began to relax before the waves in the esophagus had time to reach the stomach, and state — "the vagus impulses anticipate the esophagus needs by a good margin." Section of the vagi in the neck abolished this inhibition, and they concluded it was dependent upon the intact vagi. A similar observation was made by Veach (13) in acute experiments on cats under anesthesia. Peristalsis of the lower end of the esophagus was followed by a receptive relaxation of the

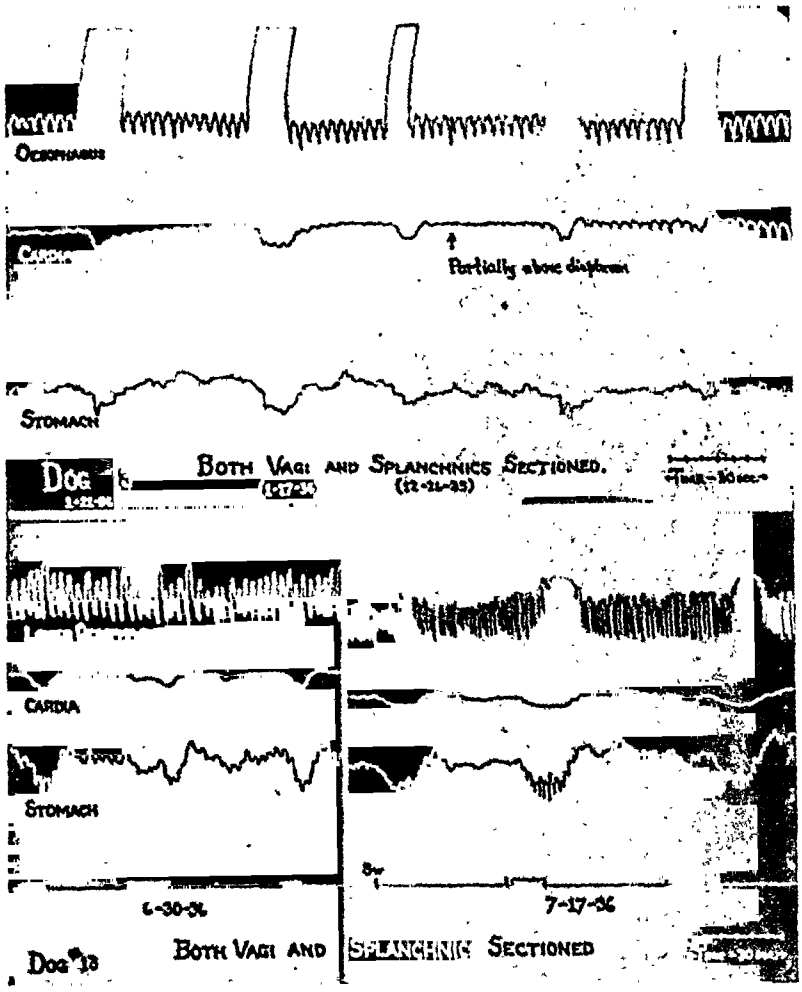


Fig. 7. Section of both vagi and both splanchnics in the thorax leaves the reflex intact. Note relaxation of the cardia and stomach upon swallowing in lower tracing.

stomach. Bilateral section of the vagi in the cervical region abolished this relaxation. He suggested that the myenteric plexus may not function as regards this phenomenon and the intact vagi are essential. Our observations on dogs, which animal has comparatively little smooth muscle in the esophagus, confirm the disappearance of this reflex following high vagus section, but in this animal we may assume that no peristaltic wave under these circumstances arises even in the lower esophagus. Consequently, if this phenomenon of relaxation is dependent upon a reflex process in the esophagus, the key to the mechanism has been lost when the esophagus is paralyzed.

That the vagi exercise a regulatory function as regards the activity of the cardia is agreed by all investigators. Krehl (14) cut the vagi below the diaphragm in dogs and found the esophagus to have lost a part of its tone and the cardia to be patulous. He tested the tonus of the cardia by inserting a stomach tube through the opening by way of a gastrostomy. Sinnhuber (16), who also worked on dogs, concluded that section of the vagi above but close to the diaphragm renders the cardia atonic. These observations differ from those of Knight, who felt section of the vagi merely removed the powers of inhibition in the sphincter. In all of our animals with vagi sectioned in the thorax, the cardia seemed to remain practically unaffected in tone and never was the power of relaxation lost. It may be, however, that this animal differs in this respect from the cat used by Knight. He felt that when the sympathetics were also sectioned, the cardia was again free to relax under intrinsic control. The influence of the sympathetics did not seem to be of importance in this respect in our observations. Whether the splanchnics were sectioned or the sympathetic fibers cut about the left gastric artery, relaxation of the cardia and stomach were little affected. This was true whether or not the vagi were intact or sectioned in the thorax. This would lead one to conclude with M'Swiney (15) that the cardia and upper portion of the stomach are closely related in function and that the cardia is less associated with changes of tonus in the esophagus. The separateness of the activity of the cardia has impressed us in these observations. It does not seem necessary that a peristaltic wave actually approach the cardia in order for

that sphincter to undergo inhibition. On the other hand it does seem necessary that some sort of reflex be initiated in the esophagus before this relaxation actually takes place. We are forced then to appreciate the dependence of its activity upon the extrinsically innervated esophagus. There are two possibilities in which this correlation of activity could take place under the circumstances of our experiments. Either section of the vagi in the thorax leaves connection along the esophageal wall with the vagus above the section that is effective in carrying out the reflex (long vagus fibers), or the dog has a myenteric plexus in the esophagus with which the vagus above the section makes contact and by which it relays impulses to the cardia.

SUMMARY AND CONCLUSIONS

By the use of balloons it was possible to make a careful study of the activity of the esophagus, cardia and stomach, without the use of an anesthetic, in dogs with gastric and esophageal fistulae. Either deglutition or a secondary peristaltic wave of the esophagus initiated by distending an esophageal balloon, is effective in inducing a relaxation of the cardia and stomach. Even though this wave may appear to die out before reaching the cardia, inhibition takes place. Reflex inhibition is always begun before the wave in the esophagus has had time to reach the cardia. This would indicate that in deglutition and in stimulating the esophagus by a balloon nerve impulses reach the cardia and elicit inhibition at once. A peristaltic wave may or may not follow. If these impulses travel by way of long vagus fibers, such fibers must be given off above the hilus of the lung. Thus nerve impulses might reach the cardia directly by long fibers in the esophageal wall or by way of cells of Auerbach.

The cardiac sphincter in the dog is not materially affected in tonus or powers of relaxation by section of the vagi in the thorax or by section of the sympathetics. No marked spasm and no paralysis was observed immediately following or months after such nerve section. Double vagotomy in the thorax followed by section of the sympathetics gave similar results. Section of one vagus trunk in the cervical region while raising the threshold for initiation of a wave in the esophagus, did not otherwise affect the relaxation of the cardia and stomach. Section of both vagi in the cervical region results in a paralyzed esophagus and an inability to elicit inhibition of the cardia. The tone of the cardia, at first, was slightly decreased by this operation but later regained, while the stomach tended to become hypertonic.

Receptive relaxation would not seem to be dependent upon the vagi alone if cutting these trunks in the thorax means that all vagus fibers to the cardia and stomach have been interrupted. The reflex is abolished when the vagi are sectioned in the cervical region but the esophagus is paralyzed by this operation. Consequently the nervous relationship between the esophagus and cardia has been destroyed.

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Editorials

PERSONS WHO CANNOT WEAR DENTAL PLATES

EVERY so often one sees a woman without teeth. Ask her why she isn't wearing plates and the answer is that she has three or four sets but she cannot stand any one of them in her mouth. Perhaps she pulls two or three out of her handbag to show how bad they are and where several dentists have ground away the material in an effort to remove pressure points. If she is a woman of means, one of the pairs of plates will almost certainly be made of gold, perhaps a beautiful example of the dentist's art, but no more comfortable to wear than the others.

When one asks such a patient for more details as to why she can't wear the plates she answers that they burn her palate, or they don't seem to fit, or they gag her, or she can never forget that they are in her mouth, or they make her terribly nervous.

After one has met a number of these women one can begin to see that they fall into a type: they are all hypersensitive and fussy and nervous; everything annoys them, and they are full of aches and pains. Not infrequently one finds on questioning them that they never could brush their back teeth without getting nauseated. As one might expect, after their teeth are out they go from one dentist to another, hoping always to find some paragon who will either make a new and satisfactory plate, or will so adjust one of the old plates that it will be comfortable in the mouth. Actually, no one ever seems to be able to help them, and this is not surprising when one comes to realize that the trouble is with them and not with the plates.

Obviously the lesson each physician must learn

Preliminary Program of Annual Meeting of the American Gastro-Enterological Association

MONDAY, JUNE 7, 1937

MORNING SESSION, 9:00 A. M.
(Daylight Saving Time)

MEMORIAL ADDRESSES
of
Dr. Henry Plummer, Dr. Sidney Simon, Dr. Frank Smithies

PRESIDENTIAL ADDRESS
Dr. Chester M. Jones, Boston, Mass.

1. "The Influence of the Extrinsic Innervation on the Human Gastric Motor Mechanism"
   Dr. Louis E. Barron (by invitation) Columbus, Ohio

2. "Experimental Studies in Gastric Physiology in Man"
   V. Influence of Osmotic Tension in the Duodenum on Pyloric Action and Gastric Evacuation
   Dr. J. Gershon-Cohen (by invitation) Philadelphia, Pa.
   Dr. Harry Shay, Philadelphia, Pa.

3. "A Theory on the Formation of Peptic Ulcer"
   Dr. Heinrich Necheles, Chicago, Illinois

4. "Massive Gastric Hemorrhage"
   Dr. John M. Blackford, Seattle, Wash.

5. "Hemorrhagic Gastritis: A Gastroscopic Study"
   Dr. Edward B. Benedict (by invitation) Boston, Mass.

THE ALVAREZ LECTURE
(Founded in 1929 by Dr. Frank Smithies)
Dr. Raoul Bensaude of Paris, has been invited to deliver the Alvarez Lecture

Adjournment for Luncheon

2:30 P. M.

6. "Cinefluorographic Studies of Lesions of the Gastro-Intestinal Tract"
   Dr. Dewitt Stetten, New York, N. Y.
   Dr. William H. Stewart, New York, N. Y.

7. "Observations on Gastric Acidity Before and After Development of Gastric Carcinoma"
   Dr. Mandred W. Comfort, Rochester, Minn.
   Dr. Winfield L. Butch (by invitation) Rochester, Minn.
   Dr. George B. Eusterman, Rochester, Minn.

8. "The Psychobiological Approach to Gastro-Intestinal Disorders"
   Dr. Kenneth J. Tillotson (by invitation) Cambridge, Mass.
   Instructor in Psychiatry, Harvard Medical School; Psychiatrist-in-Chief, McLean Hospital

9. "Inter-Relationship of Cardiac and Gastro-Intestinal Disorders"
   Dr. Paul D. White (by invitation) Boston, Mass.
   Lecturer on Medicine, Harvard Medical School; Physician, Massachusetts General Hospital

EXECUTIVE SESSION
(Associate members are requested not to attend)

ANNUAL DINNER, 7:30 P. M.
HOTEL CLARIDGE, ATLANTIC CITY, N. J.

TUESDAY, JUNE 8, 1937
MORNING SESSION, 9:30 A. M.

10. "Ulcer Recurrences Attributed to Upper Respiratory Tract Infection: A Possible Illustration of the Shwartzman Phenomenon"
    Dr. Burrill B. Crohn, New York, N. Y.
    Dr. Gregory Shwartzman (by invitation) New York, N. Y.

11. "Studies in Mucous Membrane Hypersensitiveness—The Allergic Reaction of the Rectal Mucous Membrane after Passive Sensitization"
    Dr. Irving Gray, Brooklyn, N. Y.
    Dr. Matthew Walzer (by invitation) Brooklyn, N. Y.

12. "Secondary Effects of Radiation Upon the Rectum Following the Treatment of Extra-rectal Pelvic Lesions"
    Dr. L. Kraeer Ferguson, Philadelphia, Pa.

13. "Deficiency States Associated with Gastro-Intestinal Diseases"
    Dr. Dwight L. Wilbur, Rochester, Minn.
    Dr. Albert M. Snell, Rochester, Minn.

14. "The Diarrhea of Diabetes" and "Steatorrhea of Pancreatic Insufficiency"
    Dr. J. Arnold Bargen, Rochester, Minn.
    Dr. Jesse L. Bollman (by invitation) Rochester, Minn.
    Dr. Edwin J. Kepler (by invitation) Rochester, Minn.

15. "The Diagnosis and Treatment of Acute Non-*Hemorrhagic Pancreatitis*"
    Dr. Robert Elman, St. Louis, Mo.

Adjournment for Luncheon

fact this is indicated by the work of Harrison and McSwiney (8).

Gastric juice of nervous or central origin is rich in both acid and pepsin. If this type of secretion is actually mediated by acetylcholine, then the latter drug, or one of its derivatives, might be of value in testing clinically for achlorhydria and achylia, and might possess an important advantage over histamine in that the reactivity of the pepsin-secreting cells might also be determined (9). It would also be of academic interest and possibly in the future of practical value to know whether or not histamine and acetylcholine act upon the same receptive mechanism in the parietal cells.

John S. Gray, Chicago, Ill.

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Book Reviews

Dietetics for the Clinician. By Milton A. Bridges, B.S., M.D., F.A.C.P. Oct., 1055 pages. Third Revised Edition. Lea & Febiger, Philadelphia. $10.00.

PREPARED with skill and obvious painstaking effort of unusual degree, and with the help of several co-authors, this volume begins with a description of the mechanics of digestion and a review of the physiology and chemistry of digestion. The vitamin factors in diet are fully described, and due allowance is made for *undiscovered* vitamins: owing to the certain presence of these latter in food, it is better to insure vitamin adequacy by prescribing foods rather than to rely solely upon special vitamin concentrates. A long chapter on the classification and structure of foods shows the sources of, requirement in, and opportunities for deficiency in, carbohydrates, fats, proteins, purins, cholesterol, minerals, water and vitamins. An extremely practical chapter on the evaluation of foods, shows the effects of cooking; the availability of food elements; and especially the therapeutic effects of food, as for example—gravies, and over-ingestion of water in the production or aggravation of gastric hypersecretion. Food adjuncts—alcohol, tea, coffee, condiments and spices—receive interesting consideration and even the effects of tobacco on diet is described. Various methods of feeding—by catheter, duodenal tube and rectal tube are detailed with suitable food prescriptions in each case. About one-half of the book is devoted to the dietetic management of diseases of adults, and this is followed by a smaller section on infant feeding and diseases of childhood. An extremely extensive "appendix" contains height and weight tables, caloric value of foods, composition of various foods and beverages, practical recipes, and bibliographies on many special topics. Finally, a general bibliography and a complete index completes a volume which, because of its reference value, deserves a place in the library of every practising physician.

Beaumont S. Cornell, Fort Wayne, Ind.

Cancer and Diet. By Frederick L. Hoffman, L.L.D. The Williams and Wilkins Company, Baltimore, Md., 1937, pp. 767, $5.00.

THE section on dietary theories of cancer etiology, while interesting, is, of necessity, confusing. The shorter section on the modern diet is intrinsically valuable, quite apart from any possible bearing on cancer. The long section on cancer metabolism will be welcomed by many readers for its convenient reference value. The balance of the book concerns an original dietary enquiry into the food habits of over 3000 cancer cases, statistically tabulated in contrast with a suitable number of non-cancer controls. The results scarcely support the author's belief that over-nutrition plays an important role in cancer etiology.

There is a growing tendency to side-step the problem of the cause of cancer by regarding the malignant process as a "mutation" utterly impregnable by all methods of investigation. Hoffman's laborious study is a refreshing antithesis to such reactionary attitude and is admirable in many points. It is unfortunate that he occasionally refers to authorities who are more or less discredited. It is unfortunate that the "dietary enquiry" method is open to so many inaccuracies. But fortunate indeed would be a world peopled with men of Hoffman's intellectual aspiration and industry.

Beaumont S. Cornell, Fort Wayne, Indiana.



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THE CREAM OF WHEAT CORPORATION

MINNEAPOLIS, MINN., U. S. A.

2:00 P. M.

16. "Back Pain in Relation to Ulcers and other Gastro-Intestinal Disturbances"

Dr. W. Jason Mixter (by invitation) Boston, Mass,

Lecturer on Neurosurgery, Harvard Medical School; Visiting Surgeon, Massachusetts General Hospital

17. "Silent Renal Pathology Presenting Gastro-Intestinal Symptoms"

**Dr. Alexander Randall (by invitation) Philadelphia, Pa.

**Professor of Urology, University of Pennsylvania.

*Dr. Boland Hughes (by invitation) Philadelphia, Pa.

18. "Quantitative Studies on the Absorption of Glucose from the Human Small Intestine"

Dr. William O. Abbott, Philadelphia, Pa.

Dr. Walter G. Karr, Philadelphia, Pa.

Dr. T. Grier Miller, Philadelphia, Pa.

19. "Deposition of Glycogen in Normal and in Experimentally Damaged Livers After Oral and Intravenous Administration of Dextrose"

Dr. Theodore L. Althausen, San Francisco, Cal.

20. "Studies on Motility of the Colon"

Dr. A. J. Carlson, Chicago, Ill.

*Associate in Urology, University of Pennsylvania.

Abstracts

ROSENBERG, DAVID H., WITH THE TECHNICAL ASSISTANCE OF WALTERS, A.

Macrocytic Anemia in Liver Disease, Particularly Cirrhosis. Observations on the incidence, course and reticulocytosis with a correlated study of the gastric acidity. Am. Jour. Med. Sci., July, 1936.

Of forty-eight patients with hepatic cirrhosis, a macrocytosis was found in 43 instances, an incidence 89.7%. It was also found in seven cases of acute toxic hepatitis, in three cases of obstructive jaundice, due to pancreatic carcinoma with extensive metastasis to the liver. In acute yellow atrophy of the liver macrocytosis was present with a normal erythrocyte count and a subnormal mean corpuscular hemoglobin concentration. A reticulocytosis varying from 1.1 to 18.0% and averaging 2.47% was found in 39 out of 62 patients. This would indicate an active erythropoiesis. The highest percentages were noted in three of the patients with the more advanced anemia. In 43 patients with icterus, 30 showed reticulocytosis, whereas in only 9 out of 19 individuals without icterus was reticulocytosis found. Achlorhydria co-existing with a macrocytic anemia may denote a deficiency of the intrinsic factor of Castle. In only 11 of 48 patients examined for their gastric acidity was a true achlorhydria found. No relationship was found between achlorhydria and macrocytic anemia in liver disease. The view of a deficient storage or utilization of the active hematopoietic principle by a defective liver seems at present to be the most tenable explanation of the macrocytic anemias in liver disease.

In summary, the authors say that in various forms of widespread or advanced hepatic disease, either a macrocytic anemia or macrocytosis alone was found in 91% of the patients. A reticulocytosis occurred in 39 patients and was more common with bilirubinemia. Macrocytosis in liver disease may possibly result from a primary swelling of the erythrocytes followed by the secondary appearance of true macrocytes.

Allen Jones, Buffalo.

WARTHEN, HARRY J. AND GRIFFIN, V. H.

"Simple Cyst of the Liver: Report of a Case." South. Med. Jour., 29:1178-1180, Dec., 1936.

Simple cysts of the liver are quite rare. Frequently the etiology, as in the case reported, can not be demonstrated but in others the lining membrane will suggest biliary or lymphatic origin. Total excision is the treatment of choice but often evacuation and marsupialization are all that can be done. In the case reported the patient was a negress 38 years of age. The illness began 9 months previous to operation with an upper respiratory infection, pain in the lower right chest, cough but no sputum, and a questionable fever. One week later the abdomen began to enlarge and within another week reached its maximum size. There was no nausea, vomiting or abdominal pain, but there was extreme weakness and during the entire 9 months an amenorrhea. Abdominal examination showed a smooth cystic mass extending from the costal margin to the pelvis. There was dullness to percussion but no fluid wave, tenderness or rigidity. Vaginal examination showed fullness in the right fornix, the cervix smooth and the fundus displaced to the left. There was marked secondary anemia and a positive blood Wassermann test. The cyst was evacuated and excised. No pedicle was found but there were numerous adhesions to the stomach and coils of intestines. An uneventful recovery occurred.

J. Duffy Hancock, Louisville.

SHERWOOD, T. C.

Relation of Season, Sex and Weight to the Basal Metabolism of the Albino Rat. Jour. Nutrit., 12, 223, 1936.

Sherwood describes variations in the basal metabolism of the Albino rat not dependent upon the seasons, body weight, sex and the sexual activity. The availability of calcium and iron in spinach is only partial according to Horwitt, Cowgill and Mendel. Three articles upon vitamin metabolism emphasize the loss of vitamin C in the cooking water in the case of Peas (Fenton, Tressler and King). When vitamin G which is obtained in alfalfa leaf meal and dried skim milk and etcetera, is included in the hen's diet there is an improvement in the hatchability of eggs which is an important fact in human dietetics because the ration of the hen directly affects the vitamin G content of the eggs produced.

Howard Frank Root, Boston.

RABINOWITCH, I. M. AND SMITH, F. C.

Metabolic Studies of Eskimos in the Canadian Eastern Arctic. Jour. Nutrit., Vol. 12, 337, Oct. 10, 1936.

The metabolic studies of Eskimos reported by Rabinowitch were carried out during the Canadian Government Eastern Arctic Patrol on the R.M.S. Nascopie. High values for non-protein nitrogen, urea nitrogen and amino-acid nitrogen occurred among the 46 cases studied, and are explained as due to the enormous quantities of meat eaten, often in a putrified state. When food is plentiful, a healthy adult may eat 5 pounds or more a day. High plasma chloride values contrasted with low con-

centrations of chloride in the urine, the latter dependent chiefly upon the absence of sodium chloride in the diet except as it naturally occurs in meat.

Polycythemia occurred in a number of Eskimos, and copper excretion in the urine was measured with the hope that some light would be thrown upon the relation of copper to hemoglobin formation. The concentration of copper was on the average four times as high in the urine of Eskimos living on the natural diet high in meat, as among Eskimos living on a diet including an appreciable amount of civilized man's food.

Glycosuria and Ketonuria were not found. The diet of the adult Eskimo in Canadian Eastern Arctic was found to contain approximately carbohydrate 40 grams, protein 250 to 300 grams and about 150 grams fat. The use of "banik," a mixture of water, baking soda and flour, especially when finances permit, tends toward a condition of alkalosis rather than the Ketosis which might be expected from the high fat diet with the absence of sodium chloride.

Blood sugar curves, performed after the ingestion of 50 grams of glucose in 13 cases showed high values (Myers-Benedict picric acid method). The average value after 30 minutes was 0.21 per cent (210 milligrams). Only six urine specimens showed traces of sugar, indicating a raised renal threshold for sugar.

The respiratory quotients were from 0.66 to 0.70 in six of ten cases, consistent with fat-protein diets. The average basal metabolism was plus 26 per cent.

No lead was found in the urine. The alleged absence of arteriosclerosis in Eskimos is denied and, therefore, other causes than lead poisoning must be found for its existence in the Eskimos.

Howard Frank Root, Boston.

CAMPBELL, W. R., FLETCHER, A. A. AND KERR, R. B.

Protamine Insulin in the Treatment of Diabetes Mellitus. Am. Jour. Med. Sci., Vol. 192, No. 5, Nov., 1936.

The authors give a summary of their experience in treating fifty cases of diabetes with Protamine Insulin. They point out that the severe diabetic, even with five doses of insulin a day, is subject to wide fluctuations from hypoglycemia to hyperglycemia especially during sleep. Protamine Insulin is absorbed slowly at the p.H. of the body tissues and depresses the blood sugar twice as long and with remarkably infrequent reactions. A case having a reaction at noon after twenty units of regular insulin before breakfast in the morning was able to take fifty units of Protamine Insulin without reaction and without any undue lowering of the blood sugar. Small increases in the dose of Protamine Insulin prolong the action without increasing the rate of fall of blood sugar. This slow fall apparently enables the patient to tolerate a blood sugar of 45 without hypoglycemic symptoms. An early morning injection of Protamine Insulin causes the lowest blood sugar reading about twelve midnight to 4:00 A. M. or about eighteen to twenty-four hours later. Accordingly, carbohydrate food is recommended in the evening or at least a shift from breakfast to the evening meal. When reactions do occur they may extend over a longer period than with regular insulin and several portions of orange juice or of bread or rice or other starchy foods may be necessary. No local reactions were observed since Protamine presumably is non-antigenic in nature.

The authors give the technique as follows:

To change from a regimen of regular insulin to Protamine Insulin 75% to 100% of the old dosage is given as a single morning injection of Protamine Insulin and for the first day 60% of regular insulin in two doses, one morning and one evening. For the second day 30% of the old dose of regular insulin in the morning and later only the Protamine Insulin each morning. The initial treatment in a new case may be carried out in the same way. Some cases will require a supplement of regular insulin and considerable individualization is necessary. There seems to be some variation in the rate of absorption of Protamine Insulin, some requiring an additional bed-time dose and others requiring a morning injection of regular insulin.

It is desirable to prevent postprandial hyperglycemia as far as possible. The amount of free insulin (now 4%) in Protamine Insulin might be varied. Protamine Insulin may be taken one to three hours before meals. The authors seem to prefer a relatively low carbohydrate diet. Overlapping of the second dose of Protamine Insulin some ten hours after the first dose helps to meet the postprandial rise. In some cases, too, the regular insulin in the morning, and the evening dose of Protamine Insulin maintains a blood sugar at the lowest constant level and in this way provides the greatest degree of functional rest to the pancreas. With regular insulin, especially in its purest form, three-fifths of the day there is no functional support of the pancreas and hence no aid in building up a carbohydrate tolerance.

For all these reasons the authors conclude that Protamine Insulin is a real contribution and will be a simpler and more economical as well as more effective form of treatment.

V. C. Rowland, Cleveland.

CASTLE, W. B. AND HAM, THOMAS HALE.

Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. J. A. M. A., Vol. 107, pp. 1456-1463, Oct. 31, 1936.

Patients with pernicious anemia appear to be unable to derive from food some substance essential for the normal function of the bone marrow. The cause of this seems to be the failure of a reaction between a substance in the food (extrinsic factor) and a substance in the normal gastric secretion (intrinsic factor). This conclusion is based on the following facts:

1. The daily administration of (extrinsic factor) 200 grams of beef muscle is without significant effect on blood formation.

2. The daily administration of (intrinsic factor) from 150 to 300 c.c. of normal human gastric juice is without significant effect on blood formation.

3. If, however, such amounts of each substance are administered daily in such a way as to permit contact either before or after administration, chemical improvement and evidence of increased blood formation are apparent within ten days and are progressive for the duration of such therapy.

In a recent paper, Greenspon has presented the results of experiments from which he has drawn the conclusion that an extrinsic or food factor is unessential to the production of the positive effects on blood formation in pernicious anemia. He believes that the authors' negative results with normal human gastric juice alone were due to destruction of an "antipernicious anemia principle" by peptic action during the course of preliminary incubation. In the authors' former experiments gastric juice which was not incubated before administration yielded negative results. Nevertheless the inactivity of such gastric juice, according to Greenspon, was due to peptic hydralysis in viva after administration to the patient.

The ten patients included in the present observations were all typical cases of addisonian pernicious anemia. The negative and positive effect on blood formation was determined by the reticulocyte response. The gastric juice used was from an apparently normal person and was collected after the injection of 0.5 mg. of histamine and then filtered through a coarse cloth and placed in the icebox. The patients were on a diet which contained no meat, eggs, liver or kidney. Chicken and fish were allowed once or twice a week. In six cases during the period of observation the diet was further restricted to white bread, rice, macarone, butter, potato, ice cream, tea, coffee and sugar.

The observations made were:

"Normal human gastric juice does not contain an 'antipernicious anemia principle' effective on oral administra-

tion without contact with food factor."

The technic used by Greenspon was followed except that no ice was put in the gastric juice and the time interval was lengthened to six hours. No reticulocyte or red blood cell response was noted in any of the cases. On the other hand these same patients all responded well to the administration of beef muscle and gastric juice or boiled hog mucosa and gastric juice when given simultaneously or when given ventriculin. Greenspon's result may have been due to the fact that he only excluded liver and kidney from the diet. In addition, the time interval between the giving of the gastric juice and the next meal (four hours) may not have been sufficient to prevent effective contact between the gastric juice and the food. This may be shown by the patient who was given 200 grams of beef muscle followed in six hours by 100 c.c. of gastric juice and who showed a reticulocyte response and clinical improvement. Furthermore, since the gastric juice used in this particular experiment produced positive results in conjunction with beef muscle the precautions advocated by Greenspon to prevent peptic activity are not essential to the preservation of the intrinsic factor.

"The activity of desiccated hog stomach mucosa is due to the presence of both intrinsic and extrinsic factors." This was shown by the fact that no response occurred when the intrinsic factor of hog stomach mucosa was destroyed, while the same patient responded to the oral administration of liver extract — Lilly. In addition to this, to show that extrinsic factor is present in hog stomach mucosa, the intrinsic factor was destroyed and the remainder with gastric juice fed to patients. This was followed by a reticulocyte response and clinical improvement.

It was also shown that a two hour period of incubation of gastric juice in a medium favorable for peptic hydrolysis was detrimental to the intrinsic factor, thus sustaining one of Greenspon's beliefs.

"Beef muscle and gastric juice administered without opportunity for contact are wholly ineffective." This was ascertained by feeding beef muscle and gastric juice twelve hours apart. In these cases there was no reticulocyte response until the two substances were given simultaneously.

"Former experiments apparently demonstrating the absence of extrinsic factor from certain substances are not necessarily valid." This in agreement with Greenspon is apparently due to the action of native pepsin and hydrochloric acid which results in peptic hydrolysis. However, Castle suggests that it may not be the hydrolysis but the temperature which brings about this destruction.

Francis D. Murphy, Milwaukee.

Nutritive and Therapeutic Value of the Banana (a digest of scientific literature).

The research department of the United Fruit Company who in the past have been frequently responsible for many interesting and useful additions to medical knowledge, have taken the time to produce for medical study an attractive 150 page book, in which all medical and botanical references of importance to bananas during the past few years are carefully gathered together. Just as the tomato ("love apple") was regarded as poisonous and honored only for its decorative qualities, until by slow degrees it was discovered not only to be edible, but eventually recognized as a good source of vitamins A and C, so the story of the banana reveals a long period in which, while not viewed as poisonous, it was nevertheless sternly forbidden to invalids and children. For many years indeed, we can all remember that the banana was said to be highly indigestible, and all *bona fide* lists for infant feeding had the fruit under the "don't" department. The editorial department of the Journal of the American Medical Association was among the first to come to the rescue, by showing the tremendous difference between the chemistry of the ripe and the green product. Ripening changes the high starch content to an easily absorbed carbohydrate form (soluble sugars), a process accomplished by the bananas own ferments. A ripe banana has a lot of brown in its skin but this means ripeness, not "rottenness." The inside of a banana is sterile. Bananas seldom cause allergic symptoms. The mineral content shows a very wide range of elements and the ash is alkaline. Vitamins A and C are well represented and B and G are present as well. The banana is enjoying a present vogue in many reducing diets. Its value as a food for children and adults both in health and disease deserves attention.

Beaumont S. Cornell, Fort Wayne.

GUTHRIE, J. S. AND BARGEN, J. ARNOLD.

The Effects of Drugs on Different Segments of the Intestine of Man. S. G. O., Vol. 63, No. 6, pp. 743-749, Dec., 1936.

By means of air filled balloons attached to kymographs and inserted into segments of the intestine of man, the authors were able to secure graphic tracings representing the intestinal contractions resultant from the intramuscular injection of certain drugs. The drugs studied were (1) surgical pituitrin, (2) physostigmine salicylate, (3) peristaltin or a soluble extract of cascara sagrada, grains 2½ per ampul, prepared for hypodermic injection, and (4) acetylcholine. The segments of the bowel studied were the ileum, the transverse colon and the sigmoid colon.

Of the four drugs used the authors found that pituitrin alone was a marked stimulant of the human intestine. It stimulated all segments studied and did not increase intestinal tonus. It was consistent, rapid and uniformly powerful in its action. Physostigmine in doses of 1/35 to 1/50 grain, and peristaltin caused only slight intestinal contractions in certain instances. They caused some increase in the tonus of the intestines. Acetylcholine was found to possess little worth as a stimulant of the human intestine. On 7 of 9 occasions on which it was used no evidence of any effect on the intestine was in any way apparent.

Six figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

FAULEY, G. B. AND IVY, A. C.

The Prevention of Postoperative Jejunal Ulcers by Diet and Fundusectomy. An Experimental Study in Dogs. S. G. O., Vol. 63, No. 6, pp. 717-723, Dec., 1936.

In an attempt to determine the value of fundusectomy and diet in the prevention of postoperative jejunal ulcers, the authors studied four groups of dogs. The first group was composed of 11 dogs in which the Mann-Williamson operation followed by fundusectomy was performed; they were fed on stock diet. Three developed jejunal ulcers. All lost weight so rapidly that a special diet high in nuclear substances, vitamins and carbohydrates was devised to prolong their period of postoperative survival. Group two was composed of 20 dogs who had been subjected to the Mann-Williamson operation and fundusectomy. In the 10 dogs surviving more than seventeen weeks 9 developed jejunal ulcer. In group three, 13 animals were subjected to fundusectomy, and a month later the Mann-Williamson operation, after which they were fed the special diet. None of this group developed ulcer after periods of one year in seven, and two years in six. In group four the blood supply to the fundus was ligated instead of the fundusectomy as was performed in the other groups. This procedure was not nearly as effective as fundusectomy in preventing jejunal ulcers.

From this study the authors conclude that fundusectomy and the special diet have definite value in the prevention of postoperative jejunal ulcers.

Four figures and five tables accompany the article.

Nelson M. Percy, Chicago.

The following list of abstracts throw light on the vitamin value of canned foods:*

HANNING, FLORA.

Canned Strained Vegetables as Sources of Vitamin A. 1933, J. Am. Dict. Assoc., 9, 295.

The author reported the number of milligrams of certain commercially prepared strained foods required to supply one Sherman unit of Vitamin A. Using these data the abstractor has calculated the units per gram and per ounce:

Strained Product	Sherman Units of Vitamin A Per Gram	Per Ounce
Spinach	66	1870
Carrots	25	710
Tomato	20	560
Peas	6.6	187
Green beans	4	113
Vegetable soup	6.6	187

Canned strained spinach, carrots and tomatoes were found to be excellent sources of vitamin A. Canned strained green beans, peas and vegetable soup were shown to be good sources of the vitamin. On the basis of food solids the strained canned foods were approximately equal to the raw foods as sources of vitamin A.

EDDY, WALTER H., KOHMAN, E. F. AND HALLIDAY, NELLIE.

Vitamins in Canned Food. VII. Effect of Storage on Vitamin Values of Canned Spinach. 1929, Ind. Eng. Chem., 21, 347.

A two year storage period had little effect on the vitamin C content of spinach, 4 grams affording protection at both the beginning and end of that period, although there was a slightly less growth promoting effect in the case of the stored product.

Canned spinach showed no detectable loss of vitamin A after two years' storage, 26 mg. daily permitting an average of 52 grams gain in 60 days.

1930, Michigan State Agr. Expt. Sta. Bien, Rpt., pp. 36.

Commercially canned white Country Gentleman corn fed in 7 gram amounts failed to prevent loss of weight in rats on test for vitamin A, thus indicating the presence of only a trace of the vitamin. Commercially canned yellow Golden Bantam corn, on the other hand, showed a high vitamin A content.

The yellow corn is also richer in undifferentiated vitamin B, 5 to 6 grams containing one Sherman unit; while 8 to 9 grams of white corn are required to furnish this amount.

MILLER, CAREY D.

Vitamins A and B in Fresh and Canned Pineapple. 1924, J. Home Econ., 16, 18.

Commercially canned pineapple, while slightly inferior to the fresh product in vitamin A, may be regarded as a good source of this dietary factor.

The effect of the canning process on the vitamin B content of pineapple cannot be great, as the growth curves from the canned product were only slightly inferior to those of the fresh. Both are considered good sources of vitamin B.

Rated in terms of the plus and minus signs initiated by the British Research Committee and widely used by others, the content of fresh and canned pineapple in vitamins A and B would each be indicated by the two plus signs.

HANNING, FLORA.

Further Studies of the Content of Vitamin B in Canned Strained Vegetables. 1936, J. Am. Diet. Assn., 12, 231.

Vitamin A in commercially canned strained vegetables was determined by the Sherman and Munsell assay method. The following results are expressed in International Units per gram.

Year Packed	1930-1931	1932	1933
Spinach	118	127	118
Carrots	61	63	66
Tomatoes	43	47	39
Peas	8	10	12
Green Beans	8	7	12

The Chase and Sherman method was used in the vitamin B assays with the

*These abstracts were furnished by the Research Department of the American Can Company. Editor.

A Clinically Effective Detoxifying Agent

MORRIS AND DORST REPORT THAT—"Sodium ricinoleate detoxifies many organisms in the enteric flora in vitro." . . . and "there is worthy evidence to suggest that sodium ricinoleate administered by mouth exerts a detoxifying action in the enteric flora in vivo."

BURGER STATES—"It is felt that soricin is of definite benefit in the treatment of irritable colon. . . . There is a decrease in the skin sensitivity to bacterial vaccines following treatment with soricin."

JACKSON WRITES—"I have been employing sodium ricinoleate as an intestinal detoxifying agent with most gratifying results. . . . At the moment we know of no detoxifying agent which acts so rapidly and efficiently as sodium ricinoleate."

KLINE OBSERVES—"That it (Soricin) appears to maintain the normal intestinal gradient and to reduce toxemia; and that it shows evidence of relieving the symptoms attendant upon intestinal tuberculosis without the necessity of producing purgation."

Soricin

DOSAGE FORMS: Soricin Capsules—Enteric capsules of sodium ricinoleate available in five-grain and ten-grain sizes.
Soricin Tablets—Enteric coated tablets each containing five grains of sodium ricinoleate.
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ACTION: Detoxifies in vivo • Desensitizes • Inhibits putrefaction • Prevents toxic absorption.

INDICATIONS: Bacterial Hypersensitivity of the intestinal tract • Intestinal toxemia • Intestinal allergy • Allergic diarrhea • Urticaria—angioneurotic edema • Colitis.

Literature and Sample on Request

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following results, also expressed in International Units per gram.

Year Packed	1932	1934
Tomatoes	0.42	0.25
Peas	0.12	0.29
Green Beans	0.08	0.11
Carrots	0.08	0.11
Beets	0.06	0.04
Spinach	0.05	0.06

Canned strained spinach, carrots and tomatoes were found to be good sources of vitamin A; peas and green beans also containing significant amounts. Little variation was found between different year's packs.

The vitamin B content of tomatoes and peas was found to be high and green beans, carrots, beets and spinach are valuable sources of the vitamin.

MOORE, MARGARET C. AND MOSELEY, HAL W.

A Study of Canned Shrimp with Reference to the Presence of Vitamins A, B and D. 1933, Science, 78, 368.

Vitamins A and D were shown to be present in about equal amounts in both wet-pack and dry-pack canned shrimp fat.

The animals receiving the vitamin A-free diet supplemented with 0.2-0.3 grams of shrimp fat daily grew as well as the young stock colony animals.

The animals which received 10-15 grams of the canned shrimp (0.2-0.3 grams fatty extract) daily for 13 days after their vitamin D depletion period were either entirely cured or showed marked improvement in the rachitic condition.

Vitamin B is either absent, or present in very small quantities.

HANNING, FLORA.

A Comparison of Vitamins B and G in Canned Strained Foods. 1934, J. Nutrition, 8, 449.

The samples of strained foods examined were representative of the 1931 or 1932 packs of a well known brand. The results of the studies are reported in Sherman units per ounce.

Canned Strained Food	Units of Vitamin B per Ounce	Units of Vitamin G per Ounce
Beets	3.3	3.3
Carrots	4.3	2.5
Cereal	7.5	12.0
Green Beans	4.7	6.0
Peas	7.0-8.0	7.5-8.6
Spinach	2.5	7.5-11.8
Tomato	20-24	6.7
Vegetable Soup	3.0	3.0

Of the foods examined the most potent sources of vitamin B are tomato, peas, and cereal; and the best sources of vitamin G are cereal, spinach and peas.

KOHMAN, E. F., EDDY, W. H. AND HALLIDAY, NELLIE.

Vitamins in Canned Food. VI. Strawberries. 1928, Ind. Eng. Chem., 20, 202.

Commercially canned strawberries after a year's storage were found to have a vitamin C content similar to that of fresh strawberries, which in turn are comparable to tomatoes in their content of this essential food factor. Consequently, canned strawberries can be regarded as a rich source of the antiscorbutic factor.

Strawberries are relatively low in vitamin A, being about one-fortieth as potent as tomatoes. The vitamin B content is higher, however, being about one-fourth that of tomatoes.

EDDY, W. H., KOHMAN, E. F. AND CARLSSON, VICTORIA.

Vitamins in Canned Foods. III. Canned Spinach. 1925, Ind. Eng. Chem., 17, 69.

The authors demonstrate that a com-



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mercially canned spinach is an excellent source of vitamin A. Twenty-six milligrams of canned, raw, or home cooked spinach per day meet the vitamin A requirement of the rat and produce almost normal growth. Vitamin A in spinach is not appreciably affected by canning or cooking.

Daily doses of 4.0 grams of canned spinach or 1.0 gram of raw spinach protected guinea pigs from scurvy. Home cooked spinach was not protective in daily allowances of 10.0 grams. These findings demonstrate that the vitamin C content of spinach as consumed is dependent upon the method of preparation. Commercially canned spinach has far greater antiscorbutic potency than fresh spinach cooked in an open kettle.

TODHUNTER, E. N.

A Comparison of the Vitamin G Values of Pasteurized Milk, Evaporated Milk and Eggs. 1932, J. Am. Dietetic Assoc., 8, 42.

The vitamin G content of evaporated milk (a composite of five brands available in the open market) was compared with that of pasteurized market milk by means of the Bourquin and Sherman method. Supplements of 12 ml. and 24 ml. per week of evaporated milk diluted (1:1) produced average gains of 28.5 grams and 54.1 grams respectively, as compared to gains of 30.9 grams and 52.8 grams in eight weeks produced by equal quantities of pasteurized market milk.

The author calculates that 10.1 ml. per week of diluted evaporated milk or 9.3 ml. per week of pasteurized milk produces unit growth. Expressing these values in terms of Sherman units of vitamin G per pound and per gram:

Product	Sherman Units of Vitamin G Per Pound	Per Gram
Evaporated milk diluted as per instructions on container (1:1)	300	0.66
Pasteurized milk	335	0.74

The author concluded that the vitamin G content of evaporated milk diluted (1:1) is substantially like that of pasteurized market milk.

KOHMAN, E. F., EDDY, W. H. AND GUBIN, CELIA ZALL.

Vitamins in Canned Foods. X. The Vitamin Content of Some Common Vegetables. 1931, Ind. Eng. Chem., 23, 808.

Canned turnip greens are outstandingly rich in vitamin A, being unsurpassed by any other vegetable and comparable to spinach in this respect. Twenty-five milligrams were equivalent to 5 grams of bleached or 500 mg. of unbleached celery. Canned turnip greens are not a potent source of vitamin B_1, but are a fair source of vitamin B_2 (G).

Canned turnip greens in 2-4 gram dosages proved more potent in vitamin C than 5 grams of celery, green or bleached, 10 to 15 grams of head lettuce, inner or outer leaves, or 10 grams of whole or 15 grams of shredded carrots.

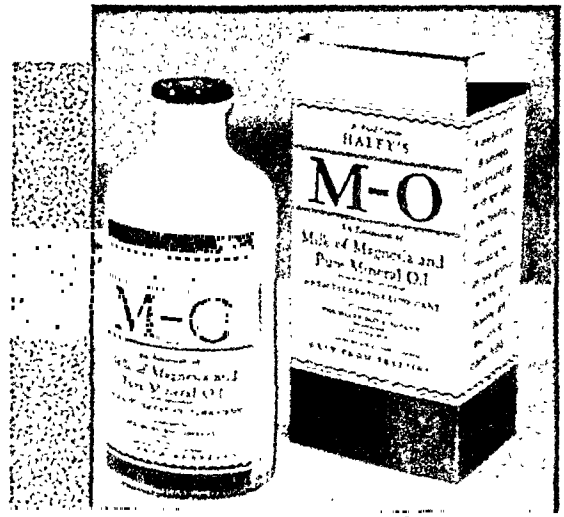
POE, C. F. AND CAMBELL, E. L.

Vitamin G Content of Commercially Canned Tomato Juice. 1933, J. Am. Dict. Assoc., 11, 343.

A modification of the Bourquin and Sherman method was used in determining the vitamin G content of some representative brands of commercially canned tomato juice. The rats were fed doses ranging from 2 ml. to 12 ml. per day.

No animals receiving 4 ml. or more of juice developed dermatitis or other symptoms of vitamin G deficiency. The vitamin G values of the 18 samples examined ranged from 0.18 to 0.28 Sherman units per ml. with an average of 0.21 units per ml. Commercially canned tomato juice contains an average

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DOSE: 1 to 2 tablespoonfuls, before breakfast and at bedtime.

Supplied in 8-oz., 16-oz., and 32-oz. bottles.

Samples to Physicians on Request

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of approximately 100 Sherman units of vitamin G per pound.

Filtered tomato juice from 4 samples of commercially canned whole juice was found to have essentially the same vitamin G content as the juice from which it was prepared.

EDDY, W. H., KOHMAN, E. F. AND CARLSSON, VICTORIA.

Vitamins in Canned Foods. IV. Green Peas. 1926, Ind. Eng. Chem., 18, 85.

Commercially canned peas are one-sixth to one-half as rich in vitamin A as butter, being closer to the latter than former value. Young peas contain more of this vitamin than the more mature ones.

The vitamin B-complex requirement for growth of the rat was met by a daily dose of 5 grams of canned peas. Larger and more mature peas contain more vitamin B-complex than smaller less mature ones.

Canned peas were shown to retain at least one-half to two-thirds of the vitamin C of raw peas. Reheating canned peas before serving did not seriously affect their antiscorbutic properties.

Commercially canned peas are an excellent source of vitamin A and a valuable source of vitamins B-complex and C in the diet.

EDDY, W. H., GURIN, CELIA ZALL AND KOHMAN, E. F.

Vitamins in Canned Foods. XII. Supplementary Nature of Grapefruit and Prunes. 1932, Ind. Eng. Chem., 24, 457.

Commercially canned prunes (Italian or French) proved to be rich in vitamin A. This product can not be considered a rich source of vitamin C. Canned prunes were approximately equivalent to milk in vitamins B and G. As in the case of milk, they contained somewhat more vitamin G than B.

The vitamin A content of canned prunes compared favorably with that of the fresh fruit. The canned product contains a smaller amount of the antiscorbutic factor than the fresh fruit.

FELLERS, CARL R.

Vitamin Content of Important Foods in the Child's Diet. 1935, Am. J. Pub. Health, 25, 1340.

Normal fresh milk and reconstituted canned milk have a small and relatively constant vitamin D content of 20 to 27 U.S.P. units per quart. The vitamin D value of milk is not altered by the processes of pasteurization, homogenization, or canning.

Two samples of irradiated canned milk were found to contain 270 U.S.P. units of vitamin D per quart, thus the reconstituted milk would contain 135 units per quart. Clinical data indicate that canned irradiated milk supplies sufficient vitamin D to prevent rickets in normal infants.

The vitamin A potency of milk is not impaired by manufacturing processes such as pasteurization, homogenization, or canning.

The vitamin A and vitamin D potencies of irradiated canned milk are of relatively much greater importance than those of vitamins B, C and G, which are also present in this product.

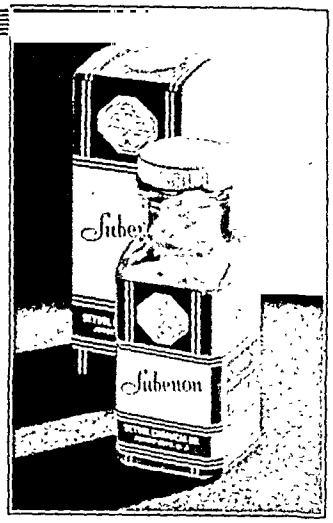
KOHMAN, E. F., EDDY, W. H. AND GURIN, CELIA ZALL.

Vitamins in Canned Foods. IX. Tomato Products. 1930, Ind. Eng. Chem., 22, 1015.

The vitamin A content of tomatoes and tomato products is practically unaffected by the commercial canning procedure, while the vitamin B content may be somewhat affected.

Vitamin C in tomatoes and tomato products is quite stable to heat, if oxidation is avoided. Any preliminary process which introduces air will result in destruction of vitamin C in proportion to the degree of exposure and the tem-

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perature to which the product is heated. The mechanics of the canning procedure provide for exclusion of oxygen with subsequent retention of vitamin C in good degree.

SAMUELS, LEO T. AND KOCH, FRED C.

The Relative Quantities of Heat-Stable and Heat-Labile Fractions of Vitamin B in Raw and Evaporated Milk.. 1932, J. Nutrition, 5, 307.

The vitamin content of commercially evaporated milk was compared with that of the frozen raw milk from which it had been made and with certified milk purchased on the open market. The frozen and certified milks had very similar antineuritic vitamin contents. The evaporated milk was found to have an antineuritic vitamin value similar to an evaporated milk composed of a mixture of two brands sold under producers' labels and two brands sold under distributors' labels.

The antineuritic vitamin content of 25 ml. of frozen raw milk was approximately the same as that of 30 ml. of milk formed by diluting (1:1) the evaporated milk to its original volume. About four-fifths to five-sixths of the antineuritic vitamin in fresh raw milk survived the processes of evaporating and canning. The heat-stable vitamin G contents of the frozen and evaporated milk were found to be practically identical.

KRAMER, MARTHA M., EDDY, WALTER H. AND KOHMAN, E. F.

Vitamins in Canned Foods. VIII. Home Canning and Commercial Canning Contrasted in their effect on Vitamin Values of Pears. 1929, Ind. Eng. Chem., 21, 859.

Pears were commercially canned with little loss of vitamin C, provided proper precautions were taken to prevent oxidation. When subjected to open-kettle and cold-pack methods of home canning, the vitamin C content of the pears was almost completely destroyed. When commercially canned without care to prevent oxidation 66 to 75 per cent of the antiscorbutic potency was retained. The absolute vitamin C value was not determined but it is thought to approximate that of apples.

The vitamin C potency of the canned product and the raw fruit from which it is prepared is apparently greatly affected by the degree of ripeness of the pears; the antiscorbutic value decreasing as the ripening process advances.

Raw or canned pears are relatively low in vitamins A and B.

KOHMAN, E. F., EDDY, W. H., CARLSSON AND HALLIDAY, NELLIE.

Vitamins in Canned Foods. V. Peaches. 1926, Ind. Eng. Chem., 18, 302.

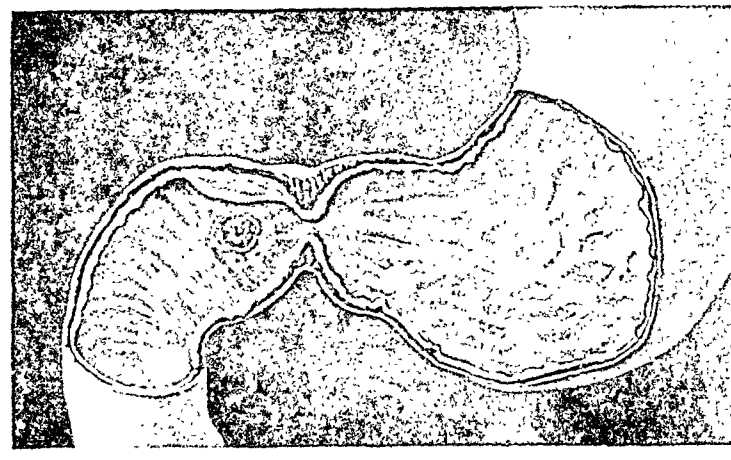
Peaches canned after removal of oxygen were found to prevent scurvy when fed in daily doses of 5 grams. Some evidence of scurvy was found in guinea pigs fed 5 grams daily of peaches canned without removal of oxygen. Commercially canned peaches as a source of vitamin C are approximately equal to raw peaches purchased on the New York market, and are far superior to peaches cooked in an open kettle. Canned peaches may be considered as a good source of the antiscorbutic vitamin.

Commercially canned peaches were found to be a good source of vitamin A. On a dry basis they are one-third to one-half as rich as butter in vitamin A. The vitamin B content of peaches was found to be negligible.

WANTED

One June, 1934, issue of the American Journal of Digestive Diseases and Nutrition. Do not send Journal but write, stating price asked, to—

Dr. Leon Schiff,
408 Doctors Bldg.,
Cincinnati, Ohio.



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The Sippy treatment, in its various modifications, is so restrictive as to be irksome to many ulcer patients. They find life a sorry burden.

Larostidin is a useful adjuvant to other treatments. When Larostidin is included there is likely to be a minimum of restriction. The diet may be rapidly increased to normal, there is no interference with the patient's business or social duties, and there is frequently a remarkable uplift of the spirit that has been smothered by the chronic infirmity.

Patients who resist a certain line of treatment often respond to a new line of attack. For example, it has been demonstrated* that 70% of the diet-alkali failures make a favorable response to Larostidin.

**Journal A.M.A.*, April 25, 1936, page 1457

HOFFMANN-LA ROCHE · INC · NUTLEY · N. J.

GUERRANT, N. B., DUTCHER, R. ADAMS, TABOR, FLORENCE S. AND RASMUSSEN, RUSSEL A.

The Vitamin Content of Canned Pineapple Juice. 1936, J. Nutrition, 11, 383.

By formal biological assay, a commercially canned pineapple juice was found to have the following vitamin values:

Vitamin A: 1 Sherman unit per 1 ml., equivalent to 30 units per ounce.

Vitamin B: 1 Sherman unit per 1.5 ml., equivalent to 20 units per ounce.

Vitamin G: 1 Sherman unit per 12 ml., equivalent to 2.5 units per ounce.

Vitamin C: 1 International unit per 0.7 ml., equivalent to 40 units per ounce.

In summary it may be said that pineapple juice is a good source of vitamins A and B, a fair source of vitamin C, and contains a small but definite quantity of vitamin G.



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Taurocol Tablets — Bile salts scientifically combined with extract of cascara sagrada, phenolphthalein and aromatics.

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Neo-Taurocol — Bile salts without phenolphthalein.

Also VERA PERLES of Sandalwood Compound indicated in certain subacute and chronic urinary diseases.

Samples on request.

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Detroit, Michigan

FELLERS, C. R., CLAGUE, J. A. AND ISHAM, P. D.

Value of Commercially Canned and Laboratory - Prepared Tomato Juices as Antiscorbutics. 1935, J. Home Econ., 27, 447.

Seven lots representing four leading brands of commercially canned tomato juice were purchased at local groceries. These tomato juices were assayed for vitamin C potency by means of the Sherman LeMer and Campbell technique.

Four samples were fully protective in daily allowances of 4 grams, and all but one sample gave complete protection from scurvy at the 6 gram level. The brand of tomato juice which failed to protect guinea pigs from scurvy at the 6 gram level in 1931, was protective at a 6 gram level in 1932, and at a 4 gram level in 1933. It is apparent that the manufacturing methods now employed in the production of commercially canned tomato juices yield products of good antiscorbutic potency.

GUERRANT, N. B., RASMUSSEN, RUSSEL A. AND DUTCHER, R. ADAMS.

The Value of the Chemical Titration Method in Determining the Vitamin C Potency of Certain Food Substances. 1935, J. Nutrition, 9, 667.

Ten samples of fresh orange juice examined by the 2,6-dichlorophenolindophenol titration method for vitamin C estimation, were found to have an average ascorbic acid content of 0.5 mg. per ml., or a calculated minimum protective dose for guinea pigs of 1.0 ml. Two samples of canned orange juice were found to have an average ascorbic content of 0.294 mg. per ml., or a calculated minimum protective dose of 1.7 ml.

These results demonstrate that canned and fresh orange juice are excellent sources of vitamin C.

MACK, M. J., FELLERS, C. R., MACLINN, W. A. AND BEAN, D. A.

Vitamin C Content of Dairy Orange Beverages. 1936, Food Research, 1, 223.

Commercially canned orange juice was found to contain 213 International Units of vitamin C per ounce compared with 228 units in fresh orange juice. These values are equivalent to protective levels of 1.33 grams and 1.24 grams for the canned and fresh juice respectively. The determinations were made by the 2,6-dichlorophenolindophenol titration method.

Biological assay confirmed these results, 215 International Units per ounce being found in the canned product and 235 units in the fresh juice.

These data indicate that canned orange juice is an excellent source of vitamin C.

CASE II
ACETANILID SERIES

A series of case types where the dominant symptom is pain of nerve origin.



The Great Sciatic Nerve, involvement of which occurs in Sciatica.

SCIATICA

CHIEF COMPLAINT: Severe pain in back of thigh, coursing down the leg. Some tender areas.

HISTORY: Occasional arthritic pains; teeth and tonsils poor: pains in thigh slight at first.

PHYSICAL: Nutrition good; slight elevation of temperature.

SYMPTOMS: Gnawing pain, often worse at night; knee-jerk increased; patient walks with knee bent.

DIAGNOSIS: Sciatica secondary to system absorption of oral infection and toxins.

TREATMENT: (Symptomatic) Acetanilid, 5 grains repeated.



Solis-Cohen and Githens regard the relief of neuralgic pains afforded by acetanilid as one of its most striking manifestations. (Pharmaco-Therapeutics).

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Bromo-Seltzer relieves pain effectively and economically.

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EMERSON DRUG COMPANY

BALTIMORE . . . . . MARYLAND

CANNON, HOWARD J. AND HIXSON, ORTON F.

Evaporated Milk—Effect of Irradiation on Vitamin A Content. 1936, Ind. Eng. Chem., 28, 1009.

The U. S. P. method of biological assay was employed to determine the vitamin A content of 2 mixtures of three nationally known brands of plain and of irradiated evaporated milk purchased on the open market.

It was found that 350 mg. of each mixture possessed the same vitamin A value as 0.5 mg. U. S. P. reference cod liver oil. Hence, both the plain and irradiated evaporated milk contained 4.28 International Units of vitamin A per gram (107 units per ounce).

GUERRANT, H. B., RASMUSSEN, RUSSEL A. AND DUTCHER, R. ADAMS.

The Value of the Chemical Titration Method in Determining the Vitamin C Potency of Certain Food Substances. 1935, J. Nutrition, 9, 667.

One sample each of fresh and canned tomato juice was tested for vitamin C by 2,6-dichlorophenolindophenol titration. The canned and fresh tomato juice contained 0.242 mg. per ml. and 0.157 mg. per ml. of ascorbic acid, respectively, with calculated minimum protective doses of 2.1 ml. and 3.2 ml. These results indicate that canned tomato juice ranks among the richest antiscorbutic foods.

HANNING, FLORA.

Comparison of the Biological and Chemical Methods for the Determination of Vitamin C in Canned Strained Vegetables and a Study of Its Variation from Year to Year. 1936, J. Nutrition, 12, 405.

Vitamin C was determined in commercially canned strained vegetables packed in growing seasons from 1930 to 1935. Assays made by the conventional guinea pig technique and by the sodium 2,6-dichlorobenzenone-indophenol titration method were in good agreement. The results, expressed in International Units of vitamin C per gram, are given in the accompanying table.

Considerable seasonal variation was noted in each product. Commercially canned tomatoes and spinach were found to be good sources and peas and green beans fair sources of vitamin C.

Product	Year Packed	International Units Vitamin C Per Gram: Bioassay	Chemical Titration
Tomatoes	1930	5.0	..
Tomatoes	1933	2.5	2.5
Tomatoes	1935		2.3
Spinach	1930	0.8	.
Fall Spinach	1931	1.0	.
Spring Spinach	1932	.6	.
Spring Spinach	1933	2.3	2.3
Spring Spinach	1934	1.8	1.8
Fall Spinach	1934	3.0	3.0
Spring Spinach	1935		1.9
Peas	1930	1.2	..
Peas	1932	1.9	..
Peas	1933	1.6	1.6
Peas	1934	1.2	1.2
Peas	1935		1.1
Green Beans	1930	0.6	.
Green Beans	1932	0.6	.
Green Beans	1933	0.8	0.8
Green Beans	1934	0.5	0.5
Green Beans	1935		0.3

GUERRANT, N. B., RASMUSSEN, RUSSEL A. AND DUTCHER, R. ADAMS.

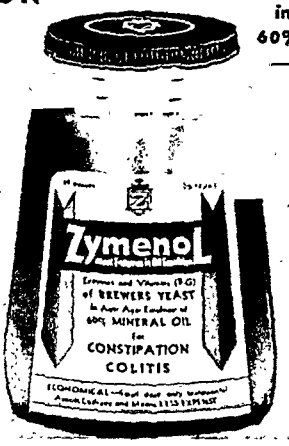
The Value of the Chemical Titration Method in Determining the Vitamin C Potency of Certain Food Substances. 1935, J. Nutrition, 9, 667.

The vitamin C content of canned pineapple juice was determined in two ways: by biological assay using guinea pigs and by 2,6-dichlorophenolindophenol titration.

The minimum protective dose was found to be seven milliliters, indicating that 0.5 mg. of ascorbic acid is present

For CONSTIPATION COLITIS

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Putrefaction is checked. The fecal mass becomes soft and bulky restoring peristalsis by natural impulse. Evacuation occurs daily without gripe, purge or irritation.

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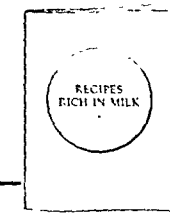
Why this is so, no one knows—and the phenomenon would be of little interest were it not that soft curd milk is more readily digestible than ordinary milk and therefore is more suitable for the delicate or disordered digestive system.

Noteworthy in this connection and of special interest to gastro-enterologists is the fact that *all* Pet Milk is soft curd milk. The quality which nature has limited to the milk of one cow in a hundred is created in *every* ounce of Pet Milk.

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in 7 ml. of canned pineapple juice. Calculated from the chemical titration data, 7 ml. was found to contain 0.616 mg. ascorbic acid, a slightly higher value than the biological assay indicated.

These potencies are equivalent to 1.4 and 1.8 International Units of vitamin C per gram of canned pineapple juice, based on the biological assay and chemical titration data, respectively.

KOHMAN, E. F., EDDY, W. H. AND GURIN, CELIA ZALL.

Vitamins in Canned Foods. XIII. Canning Tomato Juice Without Vitamin C Loss. 1933, Ind. Eng. Chem., 25, 682.

The simplicity of this new process for canning tomato juice makes it available to nearly every producer.

Due to the carbon dioxide and other gases normally present in tomatoes, ebullition was reached by heating for a few seconds at a shallow depth at a temperature far below boiling. These inert gases served to remove the oxygen which the tomatoes may contain in such a short time that no significant loss of vitamin C could occur. Tests made on three batches of tomato juice prepared from three different batches of tomatoes of uniform vitamin C potency revealed no appreciable loss of vitamin C during the process.

FELLERS, CARL R.

Vitamin Content of Important Foods in the Child's Diet. 1935, Am. J. Pub. Health, 25, 1340.

The standard Sherman technic for vitamin C was compared with the 2, 6-dichlorphenol-indephenol method for this vitamin. The values obtained by the two methods were in good agreement.

The protective levels and ascorbic acid contents are given in the following table. These figures demonstrate that canned citrus fruits and canned tomato products retain their vitamin C content in high degree.

Fruit	No. of Samples	Protective Level For Guinea Pigs Grams	Ascorbic Acid Mg. Per Gram**
Orange Juice, F....	4	1.2	0.42
Orange Juice, C....	2	1.1	0.45
Orange Slices, C....	2	1.3	0.38
Grapefruit Juices, F	2	1.3	0.38
Grapefruit Slices, C.	2	1.5	0.33
Grapefruit Juice, C.	4	1.5	0.33
Pineapple*, F	1	8.5	0.058
Pineapple*, C	2	9.2	0.054
Pineapple Juice*, C.	1	8.0	0.062
Royal Anne Cherries*, F & C .	2	24	0.021
Tomatoes, F	1	2-3	0.25-0.166
Tomatoes, C.....	2	2.5-5	0.20-0.10
Tomato Juice, C....	13	2-7	0.25-0.071
Pureed Tomato*, C.	2	3.5	0.14
Elberta Peaches*, F.	1	11	0.045
Peaches*, C	2	12	0.041
Prune Juice*, C.....	1	50	0.01

*—Determined by titration method using pure ascorbic acid as standard
**—Calculated by abstractor
C—Commercially canned
F—Fresh.

FELLERS, CARL R.

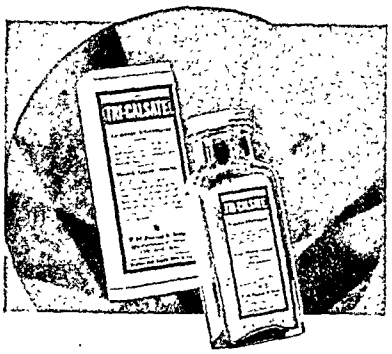
Vitamin Content of Important Foods in the Child's Diet. 1935, Am. J. Pub. Health, 25, 1340.

In addition to minerals and cellulose materials, vegetables are valuable as sources of the vitamins. The process of canning non-acid vegetables usually causes a loss of 60 to 90 per cent of the vitamin C of fresh vegetables. In spite of these losses, canned, whole or sieved vegetables are of distinct antiscorbutic value. The vitamin C contents of a few fresh canned vegetables are included in the table.

Vegetable	No. of Samples	Protective Level For Guinea Pigs Grams	Ascorbic Acid** Mg. per Gram
Peas, C	13	8.8	0.057
Sieved Peas*, C	4	14.6	0.034
Green Asparagus, C	3	10.0	0.05
Spinach, C ...	5	7.5	0.066
Sieved Spinach*, C.	4	5.5	0.091
Snap Beans*, C	2	13.0	0.038
Sieved Snap Beans*, C ..	2	15.0	0.033
Lima Beans, C	7	8.5	0.058
Sieved Beets, C	2	13.0	0.038

C—Commercially canned
*—Determined by titration method using pure ascorbic acid as standard
**—Calculated by abstractor

The heat treatment employed in canning vegetables does not seriously alter the vitamin A, B, or G content.



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Neutralizes Without Harmful Alkalosis

TRI-CALSATE

Tri-Calsate neutralizes excess gastric HCL yet does not cause a rebound in acidity or alkalize the stomach contents. The buffering effect of its end salts protects against a harmful alkalosis.

Non-toxic, non-irritating. Palatable, granular, effervescent . . . leaves the kidneys unharmed.

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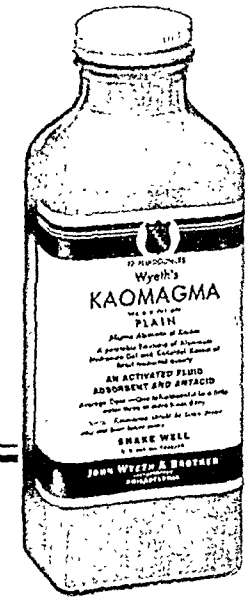
MAGMA ALUMINAE ET KAOLINI

- *adsorbs intestinal toxins*
- *checks diarrhea*
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KAOMAGMA is a preparation of finest medicinal kaolin *activated to many times its normal adsorptive potency* by fluid dispersion in alumina gel. Kaomagma consolidates liquid stools and prevents the fluid depletion encountered in diarrheal conditions. It adsorbs gas, mucus and bacterial toxins, preventing further irritation to the intestinal mucosa. At the same time its definitely soothing and protective action upon the lining of the intestines allays inflammation, reduces soreness and discomfort, and hastens the return of normal bowel function.

AVAILABLE IN TWO FORMS:

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PEPTIC ULCER

Symptomatic Relief — the most important problem in the patients *mind* — is accomplished almost immediately when Creamalin is used in peptic ulcer. Epigastric pain promptly subsides with the first dose, and is held in dependable abeyance thereafter. Hyperperistalsis and pylorospasm are overcome, and the patient experiences complete subjective relief, with cessation of all symptoms in 24 hours.

Under Creamalin therapy, healing of peptic ulcer is unusually rapid. All roentgenologic evidence of the ulcer crater disappears in 7 to 12 days when Creamalin is administered by the "continuous drip" method, and in 3 to 6 weeks under oral administration.

Creamalin is a distinctive colloidal cream of aluminum hydroxide, notable for its acid-fixing powers. It neutralizes by adsorption 12 times its volume of N/10 HCl in less than 30 minutes (direct titration, Toepfer's reagent). Complete and sustained neutralization of the acid gastric juice, and consequently rapid healing, are thus assured. As the aluminum hydroxide is not absorbed systemically, alkalosis becomes impossible. Creamalin does not produce a secondary rise in acid gastric juice secretion.

Creamalin is indicated in the treatment of peptic ulcer, hyperacidity, and jejunal ulcers following gastro-enterostomy. Detailed literature, reprints of published reports, and clinical test samples on request.

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3616 Euclid Avenue
Cleveland, Ohio

Creamalin

HESS, ALFRED F.

Recent Advances in Knowledge of Scurvy and the Antiscorbutic Vitamin. 1932, J. Am. Med. Assoc., 98, 1429.

Prior to 1917 a diet of dried or canned foods was believed to lead to the development of scurvy. In 1918, it was shown that canned tomatoes retained the major portion of their vitamin C. Shortly after this Dr. Hess demonstrated that the factor responsible for the destruction of vitamin C was oxidation rather than heat, and what has commonly been considered the damaging effect of high temperature was largely the effect of oxidation. This discovery precipitated the studies of Kohman and Eddy and their collaborators, which have shown that vegetables and fruits can be canned with very slight loss of the antiscorbutic factor, if the deleterius effect of oxygen is excluded.

DANIEL, ESTHER P., KENNEDY, MARY H. AND MUNSELL, HAZEL E.

Relative Vitamin C Content of Orange and Tomato Juices Determined Chemically and Biologically. 1936, J. Home Econ., 28, 470.

Commercially canned tomatoes packed in New York State and labeled "Grade C" were strained and the juice assayed for ascorbic acid potency. The biological assays were carried out according to the Sherman et al, guinea pig procedure. The chemical titration method of Bessey and King was followed.

The minimum protective dose determined biologically was found to be about 3 ml., which compares favorably with 2.4 ml., the average minimum protective dose calculated from the results of the chemical titration. The average ascorbic acid content was found to be 0.21 mg. per ml. equivalent to 4 International Units per gram.

Thus, canned tomatoes rank high among foods in antiscorbutic value.

LAMER, V. K., CAMPBELL, H. L. AND SHERMAN, H. C.

The Effect of Temperature and the Concentration of Hydrogen Ions Upon the Rate of Destruction of Antiscorbutic Vitamin (Vitamin C). 1922, J. Am. Chem. Soc., 44, 172.

Juice from commercially canned tomatoes was used as the sole source of vitamin C in the work described in this paper because of its high concentration of this vitamin, and the uniform antiscorbutic potency to be found in tomatoes of the same lot.

Three ml. of the juice expressed from canned tomatoes was adequate for complete protection, which ranks canned tomatoes as one of the best sources of vitamin C.

GUERRANT, N. B., RASMUSSEN, RUSSEL A. AND DUTCHER, R. ADAMS.

The Value of the Chemical Titration Method in Determining the Vitamin C Potency of Certain Food Substances. 1935, J. Nutrition, 9, 667.

One sample each of fresh and canned grapefruit juice was assayed for vitamin C by the 2,6-dichlorophenolindophenol titration. The canned and fresh juice contained 0.41 mg. per ml. and 0.266 mg. per ml. of ascorbic acid, respectively, with calculated minimum protective doses of 1.2 ml. and 1.9 ml. These data indicate that both canned and fresh grapefruit juice are excellent sources of vitamin C.

FELLERS, CARL R. AND ISHAM, PAUL D.

Vitamin C in Canned Citrus Products. 1932, J. Home. Econ., 24, 826.

One gram per day (6 days a week) of canned orange juice gave full protection against scurvy over a 90-day test period; hence it must be ranked as one of the best food sources of vitamin C.

Since canned orange slices gave protection at slightly more than the 1 gram feeding level, this product must also be considered as an excellent vitamin C carrier.

The fruit used in this experiment had undergone from 6 to 9 months storage.

DAGGS, RAY G. AND EATON, A. G.

Vitamin C Content of Canned Tomato Juice. 1934, Ind. Eng. Chem., 26, 292.

The destruction of vitamin C which may occur during the canning process is slight indeed when one considers the ease with which this vitamin is oxidized.

Four milliliters of the commercial product or of the fresh juice from which it was made gave complete protection, while 3 ml. of the canned or the fresh juice, resulted in the development of mild symptoms of scurvy in guinea pigs.

MACLEOD, GRACE AND BOOHER, LELA.

The Antiscorbutic Content of Some Preserved Foods. 1930, J. Home Econ., 22, 588.

Only the pulp of the canned pimiento was tested, the juice being drained off as is usually the practice in the household use of this product.

The protective level for canned pimiento pulp was found to be 2 grams, the same as that obtained for fresh grapefruit. This indicates a potency of 227 Sherman units per pound. Canned pimiento, therefore, ranks as one of the richest antiscorbutic foods.



» » EXERCISE « «

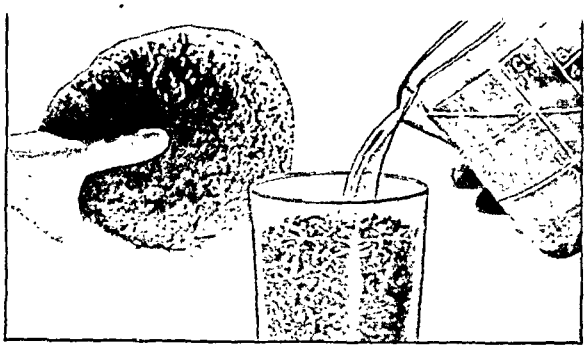
Exercise is one of the important factors in the treatment of constipation. Of equal importance are suitable diet and a regular habit time for bowel movement. Unfortunately, under the present mode of living, such strict regimen is difficult to enforce. While your patient may be inclined to forsake suitable diet and exercise, it is imperative that a daily bowel movement be maintained. Petrolagar assists in establishing a normal bowel movement as it mixes intimately with the feces to form a soft easily passed stool. By the use of Petrolagar habit time may be readily established and maintained.

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Petrolagar is a mechanical emulsion of pure liquid petrolatum (65% by volume) and agar-agar. Accepted by the Council on Pharmacy and Chemistry of the American Medical Association for the treatment of constipation.

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MAKE THIS TEST IN YOUR OFFICE



See ALL-BRAN absorb water like a sponge

HERE'S a test you can make in a few minutes. It shows that Kellogg's ALL-BRAN acts, in the intestinal tract, much like a water-softened sponge.

Just fill a glass four-fifths full of ALL-BRAN. Pour water up to the brim of the glass. Soak fifteen minutes, and drain off the water. Feel the water-softened mass. It's as soft as a wet sponge.

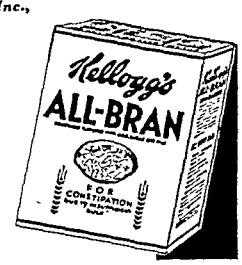
Laboratory tests* show that Kellogg's ALL-BRAN absorbs at least twice its weight in water. Within the body, this softened "bulk" gently exercises and cleanses the system.

In addition to generous "bulk," ALL-BRAN supplies vitamin B, needed for intestinal activity. ALL-BRAN also furnishes iron for the blood. This natural laxative food is more satisfactory than the continued use of pills and drugs.

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*Tests made by Samuel P. Sadtler & Son, Inc., Analytical Chemists, Philadelphia, Pa.

Serve Kellogg's ALL-BRAN regularly for regularity



Human Requirements for Vitamins—Report of the Committee on Nutritional Problems. 1934-1935 Year Book, Am. Pub. Health Assoc., 25, 69.

Clinical evidence concerning the minimum vitamin requirements of the human is rather meager. In the past there has been a multiplicity of units used in expressing vitamin units in food products. The adoption of International units for vitamins A, B, C and D will help to simplify this in the future. The values given for vitamin requirements are those that prevent the appearance of clinical evidences of deficiency, but do not allow for a liberal allowance which may be desirable or even necessary for protection against deficiencies that have less well defined symptoms.

Vitainm A

One Sherman unit of vitamin A is equivalent to 1.4 International units. The minimum vitamin A requirement of an infant is probably close to 1500 International units per day. This amount is supplied by 750 ml. of human milk of the highest potency. Larger children and adults probably require increased amounts of vitamin A, but the exact quantities can only be postulated.

Vitamin B

In this country the occurrence of severe vitamin B deficiency, or beriberi, is extremely rare. The minimum daily requirement of vitamin B gradually increases from approximately 50 International units for infants to 200 for adults.

Vitamin C

The minimum amount of vitamin C required to protect an infant from scurvy is probably 100 International units per day. For adults the minimum protective dose is about 300 International units, equivalent to 15 milligrams of active ascorbic acid.

Vitamin D

The requirement of the infant has been fairly well established for vitamin D, as long as cod liver oil is used as the source of the vitamin. The minimum daily dose that will protect an infant from rickets is 250 Steenbock or 700 International units. The need for this vitamin is greatest during the first two years, after which it is greatly diminished. Various sources of vitamin D such as cod liver oil, irradiated ergosterol, and irradiated cholesterol do not possess the same relative values for the cure or prevention of rickets in rats and children.

Pellagra Preventing Factor

Methods used for the evaluation of vitamin G have not been a satisfactory measure of the pellagra preventive value of a food. There are probably several growth promoting factors present in vitamin G containing foods. Thirty grams of dried yeast daily, supplies the smallest amount of the factor or factors required for the prevention of pellagra.

Vitamin E

There is no conclusive evidence that vitamin E is required by the human. If this vitamin is essential it is probably adequately supplied in the diet.

PARSONS, HELEN AND STINE, LOIS.

Yellow Sweet Corn Has More Vitamin A Than White Corn. 1932, Agr. Exp. Sta., Univ. Wisc., Bull. 421, pp. 120.

The vitamin A content of commercially canned whole grain corn of two varieties was determined by biological assay method using albino rats as the experimental animal.

Packs of Golden Bantam representing the highly pigmented yellow varieties, and White Crosby representing white varieties, were found to have widely different vitamin A values. The yellow corn proved to be a rich



Convalescence from influenza, pneumonia and other illnesses associated with winter is a slow process, frequently requiring as much care as the acute attack. The dietary management is particularly difficult. Appetite and digestion are handicapped, yet the demand for nourishing food is increased. A diet which has proved beneficial at this time is one which supplies maximum caloric value in a palatable and easily digested form.

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source of vitamin A while the white corn was almost devoid of the vitamin.

It is concluded that the average serving of this yellow sweet corn (3 ounces) contains about the same amount of vitamin A furnished by an ordinary serving of butter (1/3 to 1/4 ounce).

ASCHAM, LEAH.

The Vitamin A Content of Pimento Pepper. 1933, Georgia Exp. Sta., Bull. No. 177.

Well ripened Perfection pimento peppers were canned in a commercial cannery. The vitamin A content of the product was determined by the Sherman method of assay, using rats as the experimental animal.

Fresh pepper was fed on a comparable basis with the dry and canned product. No demonstrable loss of vitamin A potency occurred during canning. Thirty mg. of the canned product (moisture content 93.4%) was found to be equivalent in vitamin A activity to 2 mg. of the dried product, the growth response on each dosage indicating that more than one Sherman unit of vitamin A was present.

Canned pimento pepper, therefore, is one of the richest known sources of vitamin A, containing 46 International units per gm. (696 units on dry matter basis).

STEENBOCK, H. AND SCHRADER, INEZ M.

Fat Soluble Vitamins. XXXII. The Distribution of Vitamin A in Tomato and the Stability of Added Vitamin D. 1931, J. Nutrition, 4, 267.

Commercially canned tomato juice fed in daily doses of 0.25 ml. cured ophthalmia, and 0.5 ml. doses both cured ophthalmia and restored approximately normal growth in young rats depleted of vitamin A. These data demonstrate that canned whole tomato juice is a good source of vitamin A.

Tomato juice containing the pulp is 32 times as rich in vitamin A as filtered tomato juice (tomato serum).

CRIST, JOHN W. AND DYE, MARIE.

The Association of Vitamin A with Greenness in Plant Tissue. II. The Vitamin A Content of Asparagus. 1929, J. Biol. Chem., 81, 525.

Properly prepared test animals, when given 0.1 gram of canned green asparagus per day in addition to the vitamin A deficient diet, promptly recovered from the symptoms of vitamin A deficiency and grew at the rate of 32 grams in 8 weeks. A parallel test made with 0.2 gram of canned bleached asparagus resulted in rapid decline and death of the animals after the second week.

Thus, canned green asparagus is shown to be an excellent source of vitamin A while the bleached product is poor in this factor.

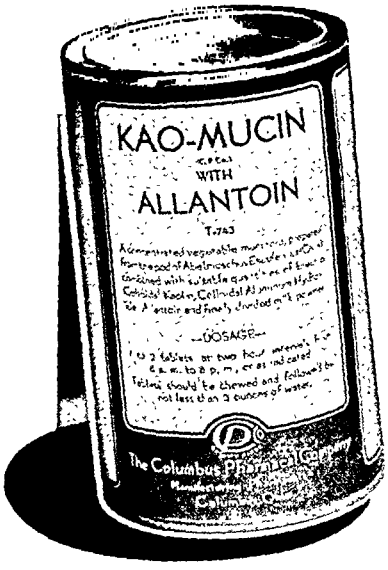
FRAPE, G. S. AND TREICHLER, RAY.

Losses of Vitamin A in Drying Fresh Raw Carrots and Sweet Potatoes and Canned Spinach. 1933, J. Agr. Res., 47, 539.

Canned spinach from which the liquid had been drained was found to contain 140 Sherman units of vitamin A per gram. This material contained only 14.7 per cent dry matter, hence, is a very potent source of vitamin A, containing 952 Sherman units per gram of solids.

Dried vegetables were reported to be inferior to raw fresh, or canned vegetables as vitamin A carriers. Upon drying: canned spinach, raw fresh carrots, and sweet potatoes lost 65, 80 and 29 per cent respectively of their vitamin A potency.

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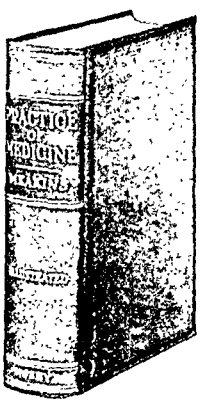
RUDOLF Schindler was born in Berlin, May 10, 1888 (parents: I. Schindler and M. Schindler, nee Simon). He attended the "K. Wilhelmsgymna-



RUDOLF SCHINDLER, M.D.

sium" in Berlin (a High School, with emphasis on classical education, Latin and Greek), where he gradu-

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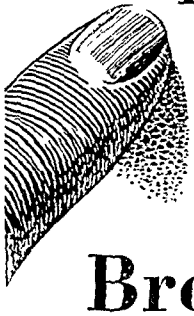
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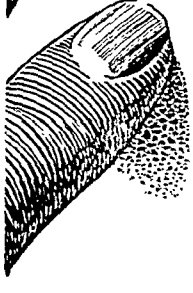
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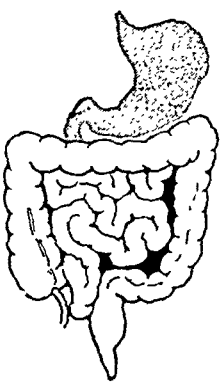


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***Ann. Int Med. 6:1465. 1933 J Lab. & Clin. Med 19:567, 1934

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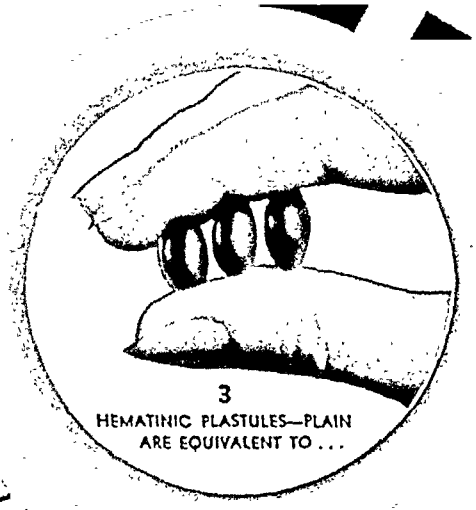
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ated in 1905. He studied medicine in Freiburg-Baden and in Berlin from 1905 to 1910. He was an Interne in the orphan asylum with Prof. Dr. Finkelstein in Berlin; in the surgical department of the Diakonissenhaus in Freiburg, Baden; and in the general Municipal Hospital of Worms. He obtained his M.D. Diploma and license in Berlin, March, 1912. After having been a country physician and ship surgeon for a few months he served in the German Army for one year. Then he got the position of Assistant in Pathology at the Municipal Hospital Munich-Schwabing with Prof. Dr. S. Oberndorfer (Oct., 1913 to August, 1914). This activity was interrupted by the outbreak of the great war. He joined the army August 3, 1914. At first he was with an Ambulance, then reported voluntarily for the service in the trenches. For a long time he remained as a physician with the 12th Bavarian Infantry Regiment, especially at the Somme and Arras; then for 6 months he was pathologist to the 6th German army. After the war he became an assistant at the Medical Department of the Hospital Munich-Schwabing (2000 beds) with Prof. Dr. Otto Neubauer. For some time he was especially interested in psychogenic internal diseases; the result were publications on the diagnosis and treatment of psychoneuroses of the intestinal tract and a book on "Nervous System and Spontaneous Hemorrhages." Because of the many unexplained cases of gastric distress which were seen daily in his department he began thinking of the possibility of gastroscopy. After some training in esophagoscopy he constructed his first rigid gastroscope in 1922; in 1923 he published the "Textbook and Atlas of Gastroscopy" which remained the standard work for 13 years. It contained 118 colored pictures of almost all anatomical changes of the gastric mucosa. In the same year a paper on gastric tumors observed by gastroscopy appeared in the Archives of Internal Medicine, Chicago, translated by his friend, the late Dr. Will Rogers of Indianapolis. From this time on he was continually teaching physicians of all countries of the world the art of gastroscopy. He recognized that the rigid tube method was too dangerous to be introduced in the general practice. He tried to contact G. Wolf, manufacturer of endoscopic instruments in Berlin. He was able to understand Dr. Schindler's suggestions and to build numerous models which never were published until finally in 1932 they succeeded in the construction of the flexible Wolf-Schindler gastroscope. In the meantime Dr. Schindler had opened a gastro-enterologic practice in Munich (1924). He has published 50 papers on psychoneuroses, the effect of certain drugs on the gastro-intestinal tract, on X-ray relief examination, gastrophotography, and especially on gastroscopy. In 1934 the University of Chicago offered him a position as a Visiting Professor of Medicine and in 1936 he was appointed Associate Clinical Professor of Medicine at the University of Chicago, Attending Gastroscopist at Michael Reese Hospital, and Consulting Gastroscopist at Cook County Hospital.

Dr. Schindler married Gabriele Schindler, nee Winkler; two of his four children died in Germany; two (a boy of 14, a girl of 6 years) are living with him in Chicago. Mrs. Schindler has helped a great deal in the development of gastroscopy, since she assisted him in each of over 3000 examinations. He does not like to perform a gastroscopy without her assistance. In the United States he has carried out and recorded over 1050 gastroscopies. Already he has many excellent pupils all over the country.

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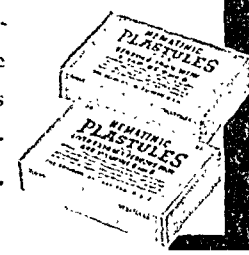


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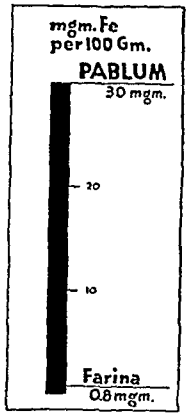
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Pablum is the only food rich in a wide variety of the accessory food factors that can be fed over long periods of time without danger of gastro-intestinal irritation. Its fiber content is only 0.9%. Yet Pablum contains 37 times more iron than farina and is an excellent source (+ + +) of vitamins B and G, in which farina is deficient. Supplying 8½ mgms. iron per ounce, Pablum is 8 times richer than spinach in iron.

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The high vitamin B content of Pablum assumes new importance in light of recent laboratory studies showing that avitaminosis B predisposes to certain gastro-intestinal disorders. Apropos of this, Cowgill says, "Gastric ulcer is another disorder which can conceivably be related to vitamin B deficiency. Insofar as the treatment of this condition usually involves a marked restriction of diet the occurrence of at least a moderate shortage of this vitamin is by no means unlikely."[2]

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a double boiler (studies *in vitro* by Ross and Burrill[3]). In addition to the above advantages, Pablum is the only base-forming cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum (Mead's Cereal thoroughly cooked) consists of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa, yeast, beef bone, iron salt and sodium chloride. [1-3] Bibliography on request.

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Carcinoma at the Cardia, a Roentgenological Discussion

By

WILLIAM H. STEWART, M.D.*

NEW YORK, NEW YORK

DR. Urban Maes of New Orleans, in a recent article in the Annals of Surgery has referred to the "Tragedy of Gastric Carcinoma." This title so aptly expresses what we see daily in any large hospital that I have been moved to use it in this discussion of carcinoma at the cardia.

It is possible to cure carcinoma of the stomach only if it is discovered early, before dissemination has occurred. There are at least a dozen reasons why carcinoma of the stomach, especially when it involves the fundus and cardia is not recognized early. Probably the most important one is that the family physician has not become sufficiently cancer conscious. He has a tendency toward optimism and too often prescribes some simple remedy and permits the patient to go without adequate study, especially if he is in a busy office or clinic. Such a patient forty-five years old or over may consult you complaining of weakness, perhaps with some slight indigestion. He may come into your office and merely say "doctor, I feel so tired," or "I am not able to play golf as I used to." Such symptoms are not alarming yet they may be the only hint that one is dealing with a gastric carcinoma, for it is true that at this time the early diagnosis can be made but only by roentgenographic examination. Do not wait until your patient has dysphagia, loss of weight and appetite, regurgitation of mucus, vomiting of blood and anemia, for these symptoms indicate that it is now too late for anything except the most radical surgery and the peril of a high mortality.

A second important reason and the most tragic of all is that carcinoma of the stomach, unless it involves the inlet or the outlet, or is well advanced, gives few symptoms except this one of weakness mentioned above. You will fully realize this when you observe the roentgen studies of the cases which illustrate the article. You will note at once that the vast majority show well-advanced lesions, practically inoperable, and yet these patients are typical of the stage of the disease that we meet daily.

What is more tragic than the following experience:

A lady on a golf course playing a full eighteen holes, while her husband is teamed up with you in a foursome; that same evening she calls on you complaining of a slight indigestion. Her husband, a doctor, has sent her with the remark: "Go over to Dr. Stewart and let him look you over, he may be able to tell you what, if anything, is wrong." When I placed her behind the fluoroscopic screen after the barium meal I saw a large inoperable carcinoma of the stomach.

It has been said that a prominent roentgenologist in the West came back from Europe feeling rather tired after attending a meeting of the International Radiological Society held in Stockholm. He complained of a few gastric symptoms but apparently nothing serious. Someone suggested that he have a series of X-ray films made. This was done and when they were placed before him on the illuminating box he saw his own stomach involved by an inoperable carcinoma. Again I say that is tragedy.

You may well ask, What are we to do about it? There is one thing that can be done and that is to advocate a routine X-ray examination in all patients of forty-five years or over who do not seem to be up to par and to repeat this examination periodically. Every one can appreciate at once the possibility of picking up a carcinoma of the stomach in its early stage by this method. Why is it not done more often? There are many reasons:

First, the physician is reluctant to send the patient to the roentgenologist because he does not wish to give the patient the impression that he is an alarmist. Many patients, when referred for X-ray examination come reluctantly believing that all this fuss is unnecessary, that the doctor is too scientific and is putting him to useless expense, when all he needs is a simple tonic. This question of expense is a serious one and often is the reason why so many patients fail to have a roentgenographic examination even when it is recommended by the family physician. Unfortunately, it is a general impression that the roentgenologist overcharges for his work. I have heard this complaint many times during my career. My answer has always been that no reliable X-ray specialist will refuse to examine any case referred to him. If asked to do so, he will gladly adjust his fee to the means of the patient.

Second, many surgeons and internists believe they can detect early carcinoma at the cardia on the fluoroscopic screen. Their experience, however, usually is limited and their negative diagnosis as a rule cannot be relied upon, for it is generally conceded that many of the finer shadows are not detected fluoroscopically and that we must rely upon the films for the detection of an early lesion. Fortunately, the better men realize the limitations of fluoroscopy so that when they have a questionable case they usually refer the patient to a competent roentgenologist for a check-up.

The third difficulty is the inexperience and unreliability of many medical men posing as specialists in roentgenology. Many of them who have opened up elaborate offices with the latest equipment and demand high fees are nevertheless not competent to make a negative diagnosis, especially in malignancy of the stomach. Some of these so-called roentgenologists are nothing more than "picture makers" and do not deserve the confidence of the medical profession. Leaders in the specialty have long recognized these conditions and have now established the American Board of Radiology which is making every effort to control this evil. All men who desire to be rated as specialists in radiology are required to pass an examination before this board. It is not easy, but it is fair. The time will soon come when all hospitals will require a certificate from this board before a staff appointment will be

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Fig. 1. E. B., female, 47 years. Three month history of indigestion, belching, heartburn, occasional vomiting. Beginning dysphagia and weight loss. *X-ray Findings:* Carcinoma of the fundus—process involves the cardia.

made. In this manner it is believed that the incompetent will gradually become eliminated.

There is an additional reason why the early diagnosis of carcinoma of the stomach is not made, namely, the slow insidiousness of the disease. It is this which often prevents the patient from consulting his physician at an early date. It has been said that investigation at the Mayo Clinic showed that *even among doctors* the average delay between the onset of the symptoms and the seeking of medical advice was fourteen months. The only way to overcome such a condition is to continue educational propaganda among the members of our profession and the general public.

What, then, is the correct technic to use in the X-ray examination of the esophago-gastric junction?

At the start it is well to appreciate that only in rare instances is the malignancy limited to the cardia. As a rule it is either a carcinoma of the esophagus spreading downward or more commonly a lesion in the fundus of the stomach spreading upward. We stress this point because there are a number of cases on record in which the upper part of the stomach was not included in the X-ray examination. As a consequence a lesion at the cardia was missed. If the esophagus is carefully examined in every case this is not likely to happen. Although this paper deals primarily with the fundus and cardiac portion of the stomach it is worth while to describe how we first examine the esophagus.

METHOD FOR ESOPHAGUS

The patient is requested to swallow a small amount of a mixture of Zoolak and barium of creamy consistency. During the act of swallowing he is observed in the right anterior oblique position under the fluoroscopic screen. As the patient continues to swallow he is rotated until a position is reached which best reveals the lesion if one is present. By means of a switchover arrangement from fluoroscopy to radiography, we immediately snap a film which will include the abnormal shadows. If satisfactory visualization is not obtained by use of the Zoolak and barium mixture, or if we are looking for varicosities or change in the rugal markings in the lower third of the esophagus we use a thick paste consisting of mucilage of acacia and barium. We have practically discarded the use of capsules except as an aid in locating non-opaque foreign bodies. They are apt to stop at any point in their downward trip without necessarily being arrested by a real organic obstruction. Any slight spasm or lack of lubrication will obstruct them and sometimes it is remarkable how long they will remain in one locality without being held by any pathologic condition.

Many extensive lesions have been found which cause little or no symptoms of dysphagia. For this reason the cardiac orifice and lower esophagus are watched with special care for any perceptible infiltration or contraction of the lumen.

The roentgenographic examination of the stomach requires a technic as exacting as any surgical procedure. A certain standardization is essential so that a lesion may not be overlooked but there must also be some necessary variation of technic whenever the pathological involvement is thereby better demonstrated. Careful preparation of the patient is essential and most important of all is that the stomach be as empty as possible when the examination is conducted.

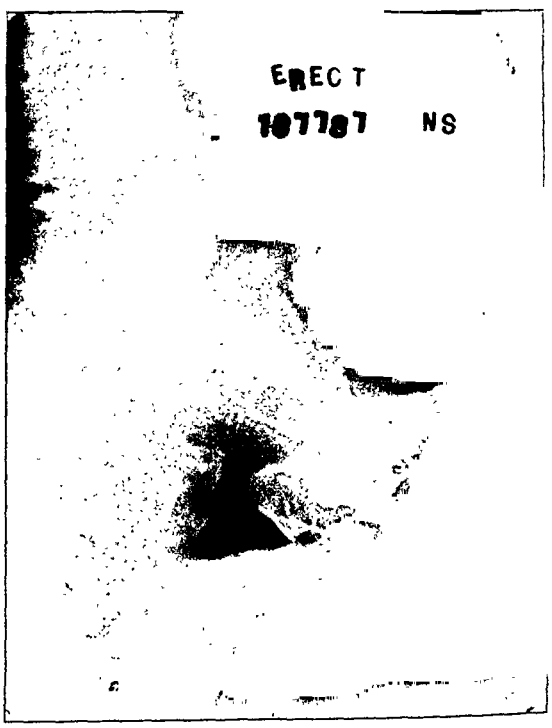


Fig. 2. N. S., male, 52 years. *Three month* history of pain, nausea and weakness with increasing dysphagia. A mass was present in the left upper quadrant. *X-ray Findings:* Extensive carcinoma of the fundus and at the cardia.



Fig. 3. J. S., male, 67 years. Burning in epigastrium for nine months. Pain and dysphagia for three months. Palpable mass in left epigastrium. *X-ray Findings:* Neoplastic involvement of cardia with dilatation of the esophagus. Autopsy showed a primary carcinoma of the splenic flexure with secondary involvement of the cardia.

METHOD FOR STOMACH

The examination of the stomach, and especially of the cardiac portion, begins as soon as the first barium enters the stomach. The patient is not permitted to take more than one swallow until certain observations are made. This barium should reach the mid portion of the stomach almost immediately, outlining the rugae and collecting in a pool in the lower stomach, leaving the cardiac end outlined by the gas bubble. By palpation the entire stomach is outlined under the screen so that the pliability of the gastric wall can be tested and some idea obtained regarding possible lesions of the anterior or posterior wall. The upper stomach is examined with special care for any abnormality in the appearance of the rugae. Tender points on palpation are localized, and masses and areas of resistance are looked for. Extrinsic masses or adhesions are sometimes more easily recognized when the stomach is only partially filled.

Special study of the gastric mucosa is carried out at this time. The pattern of the gastric mucosa is more difficult to outline than that of the colon due to the fact that complete contraction of the stomach is never present. When the colon evacuates, barium traces are left which are sufficient to outline the contracted lumen of the bowel and the appearance is rather constant and characteristic. The empty stomach is a relaxed bag and the fundus has the largest lumen of all. In addition, some slight amount of gas and watery gastric secretion are present which obscure the detail of the mucosal folds. Direct palpation is difficult because of the costal arch. The best results in the study of the gastric mucosa are obtained with only a small quantity of barium and films have the best detail when made with short exposures. Such films should be routinely made as part of every gastric examination. The relief pattern of the gastric rugae in the fundus conforms to a fairly regular standard, any marked variation or deviation from which requires careful investigation. The rugae form parallel folds producing a striped appearance, alternating with ribbons or strands of barium filling the valleys between the rugae, the entire pattern exhibiting regularity and uniformity. When organic disease is present there is marked irregularity and an abnormal or bizarre pattern may be revealed. Actual loss or absence of relief markings may be demonstrated, the parallel folds being replaced by irregular criss-crossing or radial striation, this deformity being constant. In order to diagnose early carcinoma of the posterior wall of the cardia it is necessary to obtain this visualization of the gastric rugae.

It is essential to demonstrate a normal pattern as well as normal filling of the distended stomach before a case can be reported as negative for cancerous involvement. Re-examination often is necessary and should be done more frequently if there is the least suspicion of any abnormality. There is no better method to avoid mistakes than repeating an examination regarding which there is any lingering doubt.

When a patient swallows a fluid barium meal it passes down through the esophagus at a rapid rate as far as the lower third where there is momentary hesitation before it enters the upper end of the stomach. A column of barium three or four inches high collects, and unless more is swallowed, it disappears into the stomach in a few seconds. The lower esophagus presents a constant, characteristic swaying motion as well as an additional wave motion of peristalsis. The cardiac sphincter regulates the passage of the barium into the stomach, the discharge proceding in a characteristic spurting fashion. If conditions are unusu-

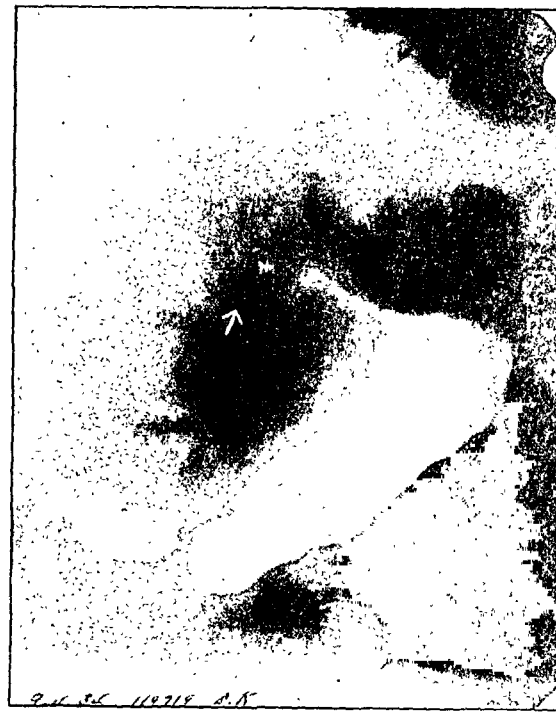


Fig. 4. D. K., male, 53 years. Epigastric pain for eight months. Thought to be angina. No dysphagia. *X-ray Findings:* Extensive malignant involvement at the cardia.



Fig. 5. A. B., male, 70 years. Nausea, vomiting, anorexia and weight loss for six months. Palpable mass in left upper quadrant. No dysphagia. *X-ray Findings:* Extensive carcinomatous involvement of the cardia without obstruction to the esophagus.

ally favorable, rugae may be visible in the lower esophagus. The length of the cardiac sphincter should be noted as well as the general outline of the esophagogastric junction.

In studying the roentgen signs indicating involvement of the cardia we must first discuss those which indicate the early lesion, and then enumerate the findings in the more advanced cases. For reasons which we have already stated, few cases have been picked up at what we call an early stage. *These have shown a slight delay in the passage of the barium through the cardia, with lack of normal spurt, the stream slowing down and giving a general impression of stiffness and induration.* This varies from a mild degree to distinct canalization. The most reliable observation is a change in the rugal markings as already described. Another finding sometimes seen is a budding projection on the lesser curvature at or near the cardia; this is rare but actually represents a cancerous crater outlined by the barium. Often there is a slight roughening and blurring along the lesser curvature as we approach the cardia. It is very significant.

The more advanced X-ray signs may be enumerated as follows:

1. Dilatation of the lower esophagus with abnormal retention of barium in its lower portion. 2. Opaque material passing through the esophageal orifice in a continuous stream. 3. Stiffness and narrowing of the esophagus or unchanging canalization through a tumor. 4. Frozen mass, the infiltration preventing the normal movements of the lower esophagus. 5. Tumor visible in gas bubble with deformity of magenblase. 6. Distorted rugal pattern with mass visible after distention of stomach by the full meal—contracted gastric lumen. 7. Forking of barium stream as it passes over the tumor. 8. Gastric hypermotility. 9. Esophageal antiperistalsis. 10. Increase in the space between the fundus and the diaphragm. 11. Roughening or projections seen on the lesser curvature near the cardia.

Let us consider each of these signs individually.

1. The lower esophagus may be dilated to twice or three times the normal size of the lumen but this dilatation is never as great as with cardiospasm. Even slight increase in the size of the lumen is of consequence and deserves study to ascertain the cause. There often is retention of barium. If the patient finds that certain solid foods, such as toast, are especially difficult to swallow, this material if obtainable, is used to test the swallowing ability, being followed by barium solution to demonstrate the obstruction.

2. Normally the esophagus discharges its contents in a peculiar, characteristic spurt-like manner. When the sphincter is infiltrated by malignant disease the fluid empties in a continuous stream. There is no preliminary hesitation of the barium in the lower esophagus but immediate and continuous emptying.

3. The sphincter is lengthened and a narrow canal is seen passing through the tumor mass. The channel as a rule is irregular and has jagged margins.

4. The mass of infiltration causes fixation of the esophagus so that the characteristic swaying and peristaltic movement of the wall is absent.

5. The gas bubble in the stomach is normally a hemispherical black shadow above the fluid level. When



Fig. 6. G. S., male, 52 years. Vague gastric symptoms, loss of weight and weakness. No dysphagia. Anemic. *X-ray Findings:* An extensive malignant growth at the cardia.



Fig. 7. F. M., male, 47 years. For last six months has had a peculiar heavy sensation in lower end of esophagus. Increased by excitement or worry. Most often appeared early in morning. No difficulty in swallowing except when eating an apple. Some weakness and loss of weight. *X-ray Findings:* Extensive malignant growth at the cardia involving at least four inches of the esophagus.

the patient is standing erect a mass may often be distinguished causing an irregular mottled density encroaching upon the inner angle of the magenblase.

6. After a swallow of a barium meal the mucosal pattern of the gastric rugae in the cardiac portion of the stomach may be seen to be altered. The normal regularity is lost and instead a bizarre, distorted, jumbled appearance may be demonstrated. When the stomach is completely filled by a full meal, the lumen in the cardiac portion is narrowed and contracted.

7. As barium trickles into the stomach the stream often forks over the mass in the cardiac portion.

8. Malignant involvement of the cardiac portion of the stomach is accompanied by hypermotility of the meal so that the stomach empties quickly; the meal pours out through the pylorus at a much accelerated rate.

9. Antiperistalsis in the lower esophagus. As many as two or three waves are simultaneously visible, depending upon the degree of obstruction.

10. Many positive cases show an unusually wide space between the top of the fundus and the left diaphragm. It is due to infiltration of the stomach wall and lack of free movement of the left diaphragm.

11. Roughening and irregularity along the lesser curvature in the region of the cardia may be noted. In addition there may be single or multiple projections in the same locality.

The clinical history and X-ray findings are of more importance in the diagnosis of gastric lesions than in many other fields of clinical investigation. A hasty roentgenographic examination without adequate knowledge of the clinical possibilities will result in a large percentage of failures. Knowledge of a physical finding or certain clinical information may be the reason for the extra effort that leads to a successful "confirmation."

Because this paper deals only with the diagnosis of carcinoma of the cardiac portion of the stomach careful consideration must be given to the differential diagnosis.

DIFFERENTIAL DIAGNOSIS

1. *Cardiospasm:* Spasm in any part of the intestinal tract is one of the most disturbing factors encountered and one of the most difficult to differentiate. Repeated examinations are often helpful in determining the permanency of the defective filling. The deformity of spasm may persist throughout several examinations and this is especially true of cardiospasm. To induce spasm, an irritant such as pepper may be given with the opaque material. The filling defect of cardiospasm occurs in the esophagus usually above the diaphragm and is typically cone-shaped or funnel-like with smooth margins. The dilatation may be extreme and even slight involvement shows greater dilatation than accompanies carcinoma. Fluid levels may be visible and splashing can be demonstrated. The clinical history and duration of the complaints usually covers a period of years. With carcinoma a mass is demonstrated producing a filling defect with ragged borders. The margins of the canal are rough, while the dilatation is slight. The barium passes through the canal in a continuous trickling stream. The history of dysphagia usually is shorter.

2. *Diverticulum of the lower esophagus is* rare. When demonstrated the shadow is disclosed beyond the lumen and it lacks any of the signs enumerated indicative of cancer.

3. *Varix* causes notching of the edge of the lower esophageal outline and masses of varices sometimes produce characteristic filling defects of the lumen with enlargement and deformity of the mucosal folds. Occasionally slight dilatation is seen.

4. *Lesions producing external pressure.* Rarely metastatic disease may form masses in close relation to the cardiac sphincter and cause dysphagia and other complaints which simulate intrinsic disease. Roentgenographically the differentiation is usually simple. The esophagus is displaced and while there may be some moderate obstruction the characteristics of malignant involvement are missing.

5. *Hernia of the diaphragm.* A part of the cardiac portion of the stomach may be invaginated into the thorax through an enlarged esophageal hiatus. This may produce dysphagia, although most of these patients have few if any symptoms and the lesion is usually an incidental finding. The hernia is best demonstrated when the patient strains while holding the breath during the time that the barium meal is in the stomach.

6. *Ulcer of the cardiac portion of the stomach.* Benign ulcer may be encountered high up on the lesser curvature or even in the lower esophagus, and occasionally in a gastric hernia. The mucal folds show radial striation. The larger the crater, the more likely is malignancy to be present, especially so if the crater

does not promptly and permanently disappear after medical treatment.

Pneumoperitoneum is occasionally of value in the differential diagnosis. If there is not too much obstruction the sausage skin method may assist in obtaining detail sufficient to recognize malignancy.

Adhesive bands may cause deformities difficult to differentiate from cancer. As a rule, they produce a smooth constriction and have a much longer history than is typical of cancer. The roentgen indications of cancer are usually absent. Weight loss is negligible.

One could hardly close this discussion without a word on the value of the esophagoscopic and gastroscopic examinations. Such instrumentation is not relished by the patients and few doctors have the ability to persuade a patient to submit to such procedure when symptoms are few and trivial. The danger of hemorrhage and rupture of the esophagus must be considered. When justifiable symptoms appear, these examinations are of great value, especially if supported by the roentgen findings. At this time, however, as already stated, it is too late for permanent surgical relief.

In this small series of twenty cases of carcinoma at the cardia, the duration of symptoms varied from six weeks to one year. Loss of weight and weakness was mentioned as a principal complaint in fifteen cases. Dysphagia was next most common, being noted in twelve. Seven cases with well marked involvement of the cardia had no dysphagia. Pain was referred to the pathological site in thirteen. Vomiting was noted in only seven and bloody vomitus in four.

We trust that we have not created the impression that we are infallible in the early roentgen diagnosis of carcinoma at the cardia. Even with the greatest possible skill certain early lesions of the cardia may be undiscovered. However, this fact should stimulate our efforts and encourage us to greater patience and persistence. Only in this way will an increased percentage of these patients have their disease discovered at a stage when radical surgery may offer a hope of cure.

Studies on the Blood Esterase*

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I

IN the rather voluminous literature which arose around the "vagusstoff" of Loewi (1) and the enzyme, choline-esterase (2), little has been reported regarding the factors which maintain and which might vary, the level of this enzyme in the blood.

These facts are well known: There are broad variations in the choline esterase level of the bloods of different species (3, 4). There are narrower, but definite, differences between individuals of the same species (4). There are differences in the choline esterase level of the blood of the same individual at different times (4, 5), independent of any known cause. There is no regular diurnal variation in the choline esterase level of the blood. There is no relationship to age, sex, or weight. It is not affected by excitement, menstruation, pregnancy, diet, exercise (5) or fasting (16).

The earlier workers have reported no relationship of the choline-esterase level of the blood to disease processes. However, from the work of Vahlquist (5) and perhaps from that of Brickner (6) there does appear to be a relationship, significant or otherwise, between the choline esterase level of the plasma and certain pathological conditions. Vahlquist (5) showed a definite low choline esterase level in long standing active tuberculosis and in other diseases producing cachexia. He also reported that patients with gastric ulcers and bronchial asthma have choline esterase levels somewhat lower than normal. However, he feels that in the latter cases ("vagotonics") the low esterase values bear no casual relationship to the conditions, since the values are not as definitely lowered as in tuberculosis. Brickner (6) has shown that in cases of active multiple sclerosis the plasma esterase is markedly decreased, that the value is highest at the beginning of periods of inactivity, that it then decreases during periods of inactivity, but never to the low level of the active cases. However, we cannot definitely attribute the low esterase level found by Brickner to a decrease in the choline-esterase since there is a difference of opinion as to the specificity of the choline-ester splitting enzyme. Stedman claims to have purified choline-esterase from plasma so that it has no effect on methyl butyrate (17). Shaw (7), believes that there are at least two esterases present in blood plasma, both capable of splitting simple esters (methyl and ethyl butyrate, tributyrin and acetylcholine), but only one of which is inhibited by eserine. He states that the purified enzyme of Stedman is not, in fact, choline-esterase since it is not inhibited by eserine. Vahlquist (5) believes that there is only one non-specific esterase in blood plasma capable of splitting choline esters as well as other simple esters. In making his titrations, Brickner used methyl butyrate as the substrate. Unfortunately, however, he did not carry on parallel titrations using acetylcholine as sub-

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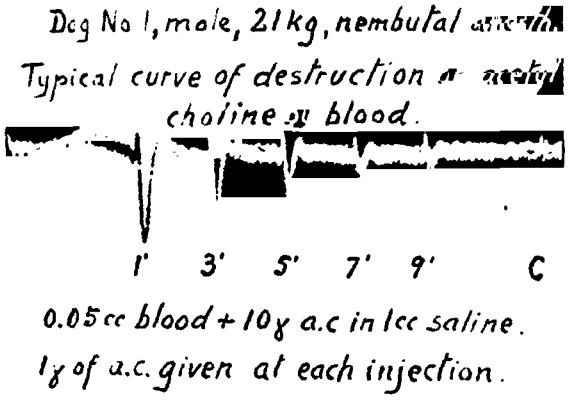


Fig. 1

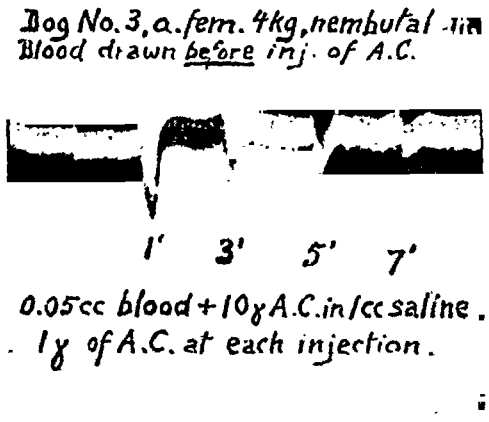


Fig. 3

strate nor did he study the effect of eserine upon this esterase.

Thus far, therefore, the above mentioned conditions are the only ones in which some change in the choline-esterase level of the blood has been postulated. In quite a number of other acute and chronic diseases, including neoplasms, no correlation has been found.

Several attempts have been reported to alter the choline-esterase level of the blood in experimental animals and man. R. Tsuji (8) found that subcutaneous injections of adrenaline, painful skin stimuli, "stimulation of the adrenals," faradic stimulation of the vagus, injection of choline intravenously, all caused a decrease in the acetylcholine splitting property of the rabbit's serum. However, samples taken at similar intervals when the rabbit had not been interfered with showed a similar fall of its choline ester splitting properties. Obviously, the author could not draw any conclusions from these findings.

Govaerts, Cambier and Van Dooren (9) found that in the dog and in man injection of acetylcholine does not change the concentration of blood esterase, and Ingvarsson confirmed this in the dog (10).

Our interest in this problem has its origin in some earlier work (11, 12, 13) in which it was shown that small doses of acetylcholine, comparable in amount with that liberated in the stomach by vagal stimulation, caused a marked contraction in the vessels of the stomach. It was indicated then that overproduction or continuous production of acetylcholine might have a causal relationship to peptic ulcer in that prolonged vascular spasm in the more susceptible areas of the stomach—the distal part of the lesser curvature and the duodenal cap which contain end arteries—might lead to anoxemia and digestion.

It was our opinion that if the factors which maintain the choline-esterase level of the blood could be determined and then experimentally altered much might be learned of the rôle of this blood esterase in maintaining the equilibrium of the autonomic nervous system and perhaps in the genesis of peptic ulcer.

Opinions as to the importance of the choline-esterase of the blood are now much at odds. Oppenheimer (14) supposed it to be a cellular waste product. Tsuji (8) believed it to be an extremely important mechanism in maintaining the balance of the vegetative processes. Vahlquist (5) questions its rôle in the finer regulations of the vegetative functions, but feels that it serves as a protective mechanism against an accumulation of acetylcholine in the blood. Brickner (6) states that the high esterase level in the blood of patients with multiple sclerosis during remissions, may be associated with repair of the myelin sheaths. Stedman (4) states that "the concentration of this

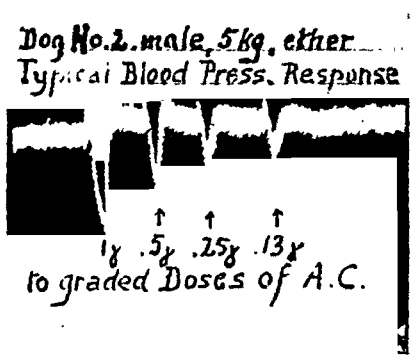


Fig. 2

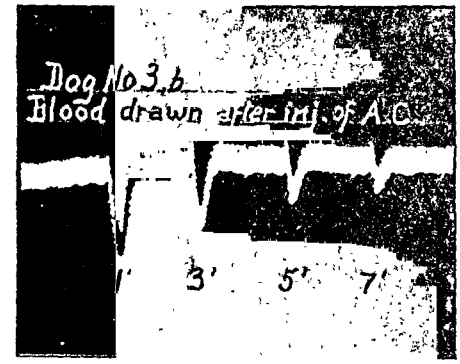


Fig. 4

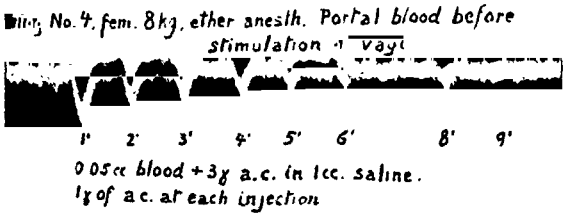


Fig. 5

enzyme in the blood must be regarded as one of the factors which control the activity of the heart. . . ."

With the purpose of observing their effect upon the choline-esterase level of the blood, the following experiments were carried out.

METHODS

The usual methods for acetylcholine assay are four in number. (1) By comparing the degree of shortening produced by a given concentration of acetylcholine when acting on muscle such as the eserinized back muscle of the leech or the frog rectus to that produced by a known concentration of acetylcholine. (2) By its effect on the perfused frog's heart. (3) By the extent of the evanescent drop in systemic blood pressure produced by intravenous injections of acetylcholine. This drop is proportional within narrow limits to the amount of acetylcholine injected. (4) By chemical methods: (a) Titration of the acetic acid produced in the hydrolysis of acetylcholine. (b) Gasometric determination of the amount of CO_2 released from carbonates (such as carbonate-Ringer solution) by the acetic acid liberated in the hydrolysis of acetylcholine.

For our purpose the third method was most suitable, since we required a method by means of which rapid and frequent assays could be carried out. By this method rather small differences in esterase level could be detected, as will be described later.

Two dogs were used for each experiment designated as subject and test dog. The experiments described below were carried out on the subject dog from which bloods were drawn before, during and after the procedures named. The enzymatic activity of these bloods were determined using the test dog. This test represents a modification of the one used by Govaerts, Cambier and Van Dooren (9).

PROCEDURE

A. Constant Injections of Acetylcholine (4 experiments performed). The effect of constant injection of acetylcholine on the esterase level of the blood was studied. The rationale of this procedure finds justification in the fact that administration of substrate often alters the elaboration of the corresponding enzyme in the organism (19).

Constant injection of acetylcholine into the femoral vein of the subject dog anesthetized with nembutal or ether was carried out by means of a modified Woodyat pump. Carotid blood pressure was recorded in the usual manner. Blood was drawn from the femoral artery, before, during and after constant injection of 375 to 600 mg. of acetylcholine over a period of about six hours. Liquoid* (0.15 mg. per c.c. blood) was added to prevent clotting.

The principle upon which the essay of choline-esterase was based is that intravenous injection of acetylcholine produces an evanescent drop of blood pressure proportional within certain narrow limits, to the amounts of acetylcholine injected, so that differences can be elicited in response to rather small variations in the amount of acetylcholine injected.

For the assay of the esterase in our blood samples, the test dog was anesthetized, one of its carotids was prepared for blood pressure recording, and one of its femoral veins was cannulated and connected by means of rubber tubing to a container from which measured quantities of saline could be released into the vein. Acetylcholine solution (10 gammas per c.c.) was prepared. The sensitivity of the test dog was determined by noting the difference in fall of blood pressure to graded doses of acetylcholine which were injected into the rubber tubing connected to the femoral vein and then washed into the vein by releasing 2-4 c.c. of saline from the container. It was generally found that variations of about 0.15 gamma can be differentiated in this manner within a range from 0.25 gamma to 2.0 gamma. The sensitivity of the dog was repeatedly tested during the experiment.

From 0.02 to 0.06 c.c. of the blood to be tested was pipetted into a watch glass, 1 c.c. of acetylcholine solution (10 gammas per c.c.) was added, and the two substances were well mixed for 15 seconds. The mixture was then drawn up into a tuberculin syringe, the needle of the syringe was introduced through the rubber tubing into the cannula of the femoral vein, 0.1 c.c. of the mixture was injected into the cannula and washed into the vein at the end of the first minute and every other minute thereafter for from 9 to 11 minutes. The first injection resulted in an evanescent drop in blood pressure almost equal to that produced by the injection of 1 gamma of acetylcholine alone, since in that short time the choline-esterase in the blood-acetylcholine mixture had not hydrolized much of the acetylcholine in the syringe. The drop in blood pressure became less with each succeeding injection due to the progressive destruction of acetylcholine by the blood with which it was mixed.

The blood drawn before an experimental procedure was tested first. An amount of this blood was used which would bring about complete destruction of the 1 c.c. of acetylcholine (10 gammas per c.c.) as shown by an absence of blood pressure response to further injection, within 9-11 minutes. The same amount of the bloods drawn during and after a given procedure was then tested against a like amount of acetylcholine. Where destruction followed a similar course, the enzymic concentration was held to be the same.

The sensitivity of this method is borne out by the following experiment, repeated many times in the course of our work. 0.05 c.c. of blood was added to 1 c.c. of acetylcholine solution (10 gammas). 0.1 c.c. of the mixture was injected at the end of 1 minute and every other minute thereafter. Complete destruction of acetylcholine was apparent at 7 minutes. 0.06 c.c. of blood produced complete destruction of the acetylcholine solution used at 5 minutes while each injection of this mixture produced a smaller drop in blood pressure than corresponding injections where 0.05 c.c. of blood was used. Likewise, definite differences were elicited when .045 c.c., .04 c.c., .035 c.c., and .03 c.c. of blood were used. (See Figs. 1, 2, 3 and 4).

Results: There is no difference in the rate at which bloods drawn before, during, and after constant injection

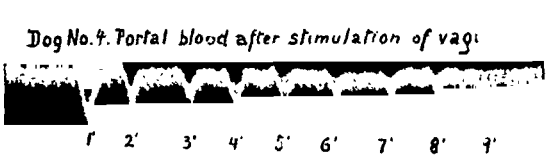


Fig. 6

*Supplied by Hoffmann-La Roche.

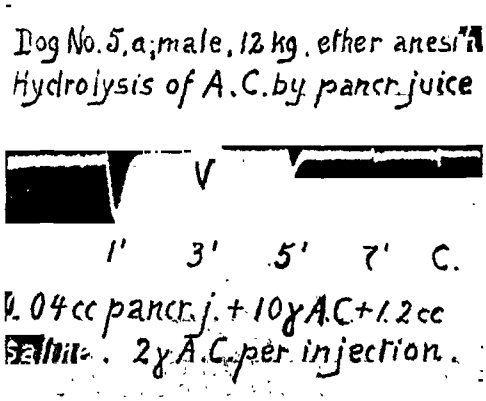


Fig. 7

of 375 to 600 mg. of acetylcholine produced hydrolysis of acetylcholine; this confirms previous work (9, 10).

B. Comparison of Bloods Drawn from Veins Leaving Various Organs (2 experiments). A few c.c.'s of blood were drawn within a few minutes from each of the following vessels: the femoral artery; femoral vein; renal vein; adrenal vein; vena cava; portal vein; splenic vein; and jugular vein of the test dog. These bloods were tested for their acetylcholine splitting power in the same manner as in the preceding experiment. This was done in order to determine whether any one organ might be the main source of choline-esterase. We realize, however, that small and possibly continuous production of esterase in one or even all organs (see Oppenheimer's theory of esterase being a waste product of cells) might not be detectable by our method.

Results: No difference was found in the rates at which these various bloods split acetylcholine.

C. Vagal Stimulation (2 experiments). Bloods were drawn from the above mentioned vessels before and after vigorous and prolonged faradic stimulation of the peripheral ends of the cut vagi in the neck.* These were tested in the usual way for their acetylcholine splitting power. The purpose of this experiment was to test the possible influence of vagus activity on the esterase concentration in the blood. (See Figs. 5 and 6).

Results: No difference was encountered in any of the bloods tested.

D. Cannulation of Pancreatic Duct (2 experiments).

As will be described below we found that pancreatic juice destroyed acetylcholine at fifteen times the rate of the blood. It was felt that should a secretion so rich in choline-esterase be diverted from the gut where it may be reabsorbed, a progressive decrease in the choline-esterase level of the blood might be the result; or that total extirpation of the pancreas as in the following experiment might result in a marked change in the blood esterase level. For this reason the following procedure was carried out. The pancreatic duct of a dog was cannulated and the pancreatic juice was collected. Fifteen c.c. of a secretin preparation was injected intravenously to stimulate flow of pancreatic juice. Blood samples were drawn from the femoral artery before and after collection of about 20 c.c. of pancreatic juice. These blood samples were tested against acetylcholine in the usual manner.

Results: No difference was found in the ability of these bloods to split acetylcholine.

E. Extirpation of the Pancreas (1 experiment).

Blood was drawn from a dog completely depancreatized one month previously and tested in the usual manner.

Result: There was no difference in the ability of this blood to destroy acetylcholine. Compared with that of normal dogs this blood was not lacking in choline esterase.

F. Reticulo-Endothelial "Blockade" (1 experiment).

A dog weighing 22 lbs. received intravenously in four days 500 c.c. of an 8% suspension of Higgins' India Ink in an attempt to block its reticulo-endothelial system. The spleen was removed, after which a sample of blood was drawn from the femoral artery. Then 100 c.c. of a 6% suspension of India Ink was injected into the femoral vein and constant injection of acetylcholine was begun. After 280 mg. of acetylcholine had been injected, a second sample of blood was drawn. These bloods were tested in the usual manner. The purpose of this experiment was to detect a possible influence of the reticulo-endothelial system on formation or destruction of esterase.

Results: No difference in the acetylcholine splitting power of these bloods were noted. Compared with the records of other dogs, there was no deficiency of esterase in the "blockaded" dog.

G. Devisceration (3 experiments).

The gut of the subject dog, from the abdominal esophagus to the lower rectum was removed, as was the spleen and pancreas. The hepatic artery and portal vein were ligated close to the liver. A sample of blood was drawn from the femoral artery after which constant injection of acetylcholine was begun. Over a period of about 3 hours from 430 to 500 mg. of acetylcholine was injected. Samples of blood were drawn during and after constant injection and these were tested for their acetylcholine splitting properties in the usual manner. This experiment was performed in order to eliminate possible effect of the liver, stomach and intestines on the formation or destruction of esterase.

Results: There was no difference in the acetylcholine splitting powers of these bloods.

II

In the course of our work we took the opportunity to test some as yet untested substances for their esterase content.

Tsuji (8) found esterase present in lymph. Plattner and Hintner (15) have reported the presence of esterase in the aqueous humour, while finding it absent in saliva, milk and urine. Vahlquist (5), Shaw (7), and Stedman (17), however, have been unable to corroberate these authors' findings of esterase in spinal fluid, using a more delicate test.

We have collected fresh pancreatic juice from dogs by cannulating the main pancreatic duct and have found that it is capable of destroying acetylcholine at about fifteen times the rate of blood. This action is entirely inhibited in the presence of 1:10,000 solution of eserine. (See Figs. 7 and 8).

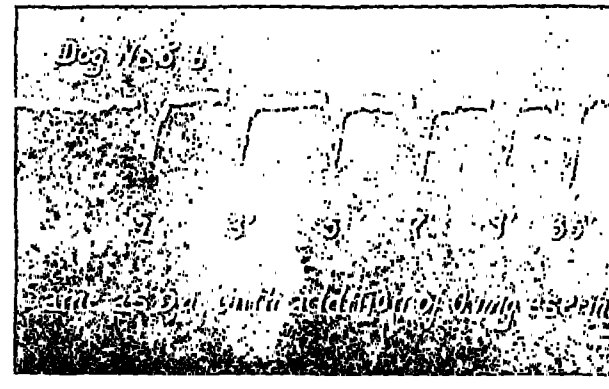


Fig. 8

*Harvard inductorium, 7 cm. coil distance, for 2 periods of 15 minutes each.

Blood free fluid from a congenital cerebellar cyst produced a rapid destruction of acetylcholine.

The urines of two nephritic patients, containing large amounts of albumin and globulin, were incapable of splitting acetylcholine. One might have expected that a kidney which is permeable to plasma proteins might also excrete esterase.

Blood-free ascites fluid produced a rapid destruction of acetylcholine.

Blood-free pus collected from the chest of a patient with empyema, was centrifuged and washed with saline. The precipitate was suspended in a small quantity of saline and tested for its acetylcholine splitting ability. It was entirely ineffective in hydrolysing acetylcholine over a period of one hour. The supernatant portion of the centrifuged pus, however, was able to split acetylcholine rapidly. A smear of the precipitate showed it to be made up almost entirely of polymorphonuclear leucocytes. Matthes (18) considers the activity of the choline-esterase of the blood to be "compatible with the action of an enzyme largely concentrated on the surface of the corpuscles," because the enzymatic activity of the cells is greater than that of the serum and also because, as Plattner and Hintner (15) have shown, swelling of cells increases their enzymatic action. Engelhart and Loewi (2) found that red cells and platelets were able to destroy acetylcholine. In the light of these findings it is interesting that pus cells apparently do not possess the choline-ester splitting property while the liquid portion of the pus with its cellular debris possesses this property to a marked extent. In spite of the high choline-esterase content of the pus, the enzyme did not become adsorbed to the cell surfaces.

SUMMARY AND CONCLUSIONS

1. Constant injection of acetylcholine, infinitely greater in quantity than that elaborated physiologically, produces no marked change in the esterase level of the blood, during approximately six hours of observation.

2. Extirpation of the spleen, pancreas, gut, liver and blocking of the reticulo-endothelial system resulted in no decrease in the esterase level of the blood during the period of observation.

3. Vigorous vagal stimulation had no effect on the esterase level of the blood.

4. Venous blood from various organs showed no differences, as tested by our method, in esterase content.

5. In the light of the above experiments it is not surprising that the esterase level shows only small variations in most normal and pathological conditions. It is felt that the esterase level of the blood is a rather immobile, unresponsive bulwark against an excess of acetylcholine in the blood.

6. Pancreatic juice has approximately fifteen times the acetylcholine splitting power of the blood. This ability is totally inhibited in the presence of eserine.

7. Ascitic fluid, fluid from a cerebellar cyst and the fluid portion of pus destroy acetylcholine.

8. Nephritic urine containing albumin and globulin, does not possess this ability, nor do washed pus cells.

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Treatment of Pylorospasm with Digitalis: Report of Five Cases

By

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THERE is a striking similarity in the innervation of the heart and the stomach. We have evidence that there is a node on the lesser curvature near the cardia which acts as a gastric pacemaker analagous to the sinoauricular node in the heart. Impulses travel by a conductive system along the lesser curvature of the stomach similar to the auriculoventricular bundle of the heart (1).

Spastic motor disturbances in peptic ulcer may be due to abnormal impulses travelling along the conductive system of the stomach. Because of the known action of digitalis in depressing the impulses in the conductive fibres of the heart, the author (2) suggested the use of digitalis in the treatment of peptic ulcer, with the expectation, that if digitalis would have a similar action on the conductive system of the stomach, spastic phenomena would be relieved.

The present paper is a report of five cases of marked pylorospasm with six hour residue that were relieved by digitalis therapy. These cases presented a similar clinical picture and were treated in a uniform manner, so they will be discussed as a group. When first seen, these patients complained of constant midepigastric pressure or burning pains from two to eight weeks in duration. They had been under treatment with alkalies without relief. None of the patients vomited spontaneously but several of them found that forced vomiting was the only means of obtaining temporary relief. All complained of loss of appetite

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Submitted December 30, 1936.

and had limited their diet to liquids and dairy foods. When the cases were first examined by means of the Roentgen-ray the stomach was atonic and ptosed; peristalsis was absent or very weak and very little barium passed through the pylorus. At six hours the gastric residue was approximately one-half to two-thirds of the original gastric content. It was not possible to determine at that time whether the obstruction at the pylorus was organic or functional, although the lack of irregularity at the antrum favored the diagnosis of functional spasm.

Digitalis was administered by the rapid method of Eggleston, calculating two minums of the tincture to the pound of body weight. Only three-quarters of the calculated dose was given, for Gold and DeGraff (3) showed that the therapeutic effects of digitalis in the heart was obtained by doses short of producing toxic effects. The dose was divided into three equal parts at 8 a.m., 2 p.m. and 8 p.m. A maintenance dose of digitalis was prescribed for the following day: four drams of the tincture to four ounces of Elixir Aromaticum. A teaspoon diluted in one-quarter glass of water was taken after meals, three times a day. No change in the diet was made and no treatment other than the administration of digitalis was given. The patients were observed every day to detect any toxic effects from the digitalis but none developed. They reported moderate relief from symptoms after the first day and complete relief after the second or third day of the digitalis therapy. Because of the marked gastric retention originally present with consequent delay in the absorption of the digitalis, the Roentgen-ray examination was not repeated until the patients reported complete relief from symptoms. In three cases the barium meal was repeated at the end of the second day and in the other two cases at the end of the third day from the start of the treatment. The examination then showed a marked increase in the tone of the stomach causing an elevation in the position of the greater curvature. The peristaltic waves were active, increased both in their rate and depth and the pyloric sphincter was functioning. At the end of six hours the stomach was completely empty. An irregular duodenal cap was present in the five cases.

CONCLUSION

Five cases of pylorospasm with six hour residue were treated by oral digitalization.

Complete relief of the pylorospasm, both in subjective and in Roentgen-ray findings was obtained in two to three days.

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The Influence of Large Doses of Vitamin D Administered Systemically and Locally on the Healing of Ulcers*

By

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SINCE it has been shown that large doses of vitamin D stimulate the metabolic rates in experimental animals (1), that it may stimulate the metabolic rates in children (2), and that an increase in the oxygen consumption occurs in the isolated muscle (3), we decided to study the influence of large doses of vitamin D in the form of viosterol administered both systemically and locally on the growth of granulation tissue. Tammann (4), working with rabbits administered simultaneously large doses of vitamin D by mouth and topically. He found that the uncovered skin ulcers in the vitamin D treated animals healed more slowly than similar controls, with degenerative changes occurring in the marginal region of the wounds giving them a bad appearance. Microscopically, many of the vessels were occluded due to a medial degeneration.

METHOD

On the backs of rabbits, circular ulcers were cut through the skin to the underlying fascia. The ulcers were cut 1 cm., 2 cm. and 5 cm. in diameter respectively in 3 groups, the 5 cm. group corresponding to those of Tammann. All of the ulcers were protected with a covering which was not in contact with the ulcer. Of the first group of animals with the 5 cm. ulcers, nine were fed viosterol,† 10,000 units per kilo, nine were untreated, six had the ulcers covered with equal amounts of viosterol (1,000,000 units per gram), and six were covered with equal amounts of non-irradiated ergosterol† in corn oil (2%) daily. Of the second group of rabbits with two ulcers 2 cm. in diameter, four had one of the ulcers covered with equal amounts of viosterol daily, and four had one of the ulcers covered with the non-irradiated ergosterol. Of the third group with ulcers 1 cm. in diameter six animals were given viosterol locally, six received the ergosterol in oil, and six were untreated.

RESULTS

Of the group of animals with the 5 cm. ulcers, those receiving viosterol by means of a stomach tube were healed in an average of 19 days with a range of variation of from 18 to 20 days. Those receiving the viosterol locally were healed in 17.6 days, with a range of 17 to 19 days, the animals receiving the non-irradiated ergosterol locally were healed in an average of 18.5 days, with a range of 17 to 20 days, while the group that was untreated was healed in 17 days, with a range of 15 to 19 days as shown in Table I. The ulcers of all of these animals were clean and the scabs firm.

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†The viosterol, and crystalline inactive ergosterol were generously provided through the courtesy of Mead Johnson & Co., Evansville, Ind.

TABLE I

Rabbits with 5 cm. ulcers

	Viosterol by mouth	Viosterol locally	Oil locally	Untreated
Average No. days required to heal.	19	17.6	18.5	17

The results of the second group of rabbits with the two cm. ulcers may be seen in Table II. The maximum variation in the number of days required to heal the ulcers was two.

The results of the third group with the ulcers 1 cm. in diameter may also be seen in Table II.

Microscopic sections taken 48 hours after the ulcers were made revealed a superficial layer of fibrin and blood cells intermingled, and beneath this a marked leukocytic infiltration with fibroblasts and newly formed capillaries. There was no demonstrable difference in the sections of any of the animals of the different groups. Sections of the healed ulcers were made and they revealed a dense connective tissue with well developed arterioles. Here again no demonstrable difference in the healed ulcers of the different groups were observed.

The animals were weighed before and after the experiment and they showed no loss in weight and did not appear dehydrated. Four of the animals died before the experiment was completed and one died the day after. Three of the deaths were in the group that was fed viosterol, one was in the untreated group, and one was in the group treated with the non-irradiated oil. In all of the cases, the cause of death was a pneumonia.

Thus, it may be seen, that in the group of animals that were fed viosterol by mouth the ulcers healed at about the same rate as the untreated ones, the average being two days slower (8%). The appearance of the ulcers both grossly and microscopically was similar to those untreated. No evidence of a stimulation of granulation tissue was observed, and the toxic effects previously described (4) were not found. The application of viosterol on the ulcers of various sizes revealed no significant differences in the rate of healing from those that were untreated. The animals receiving the non-irradiated ergosterol showed a rate of healing that closely approximated that of the animals treated with viosterol and the untreated group.

CONCLUSIONS

1. Large doses of vitamin D in the form of viosterol (1,000,00 units per gram) applied locally have no appreciable influence on the rate of healing and the character of ulcers in the rabbits.

TABLE II

		Animals receiving Viosterol on one ulcer		Animals receiving Non-irrad. oil on one ulcer		Prelim. untreated
		Viost.	Untreated	Oil	Untreated	
Ave. No. days required to heal.	Rabbits with 2 cm. ulcer.	15	14.6	16	15	11
	Rabbits with 1 cm. ulcer.	10	11.3	11	11	

2. Large doses of vitamin D by mouth produce no change in the character of the healing ulcers in the animals. The rate of healing was approximately the same as that of the controls.

3. Applications of non-irradiated ergosterol produced no appreciable changes in the rate of healing of ulcers in the rabbit.

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The Factor of Spasm in the Etiology of Jejunal Ulcer*

By

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and

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STEINBERG and Starr (1) have presented experimental evidence which indicates that spasm of the jejunal musculature is an important factor in the etiology of jejunal ulcer. Their experiment consisted of draining the duodenal secretions (pancreatic juice and bile) into the terminal ileum and of anastomosing the jejunum to the stomach. The jejunum, however, was stripped of its longitudinal and muscular coats (except that near the mesenteric border) for a distance of 10 cm. from the end-to-end gastrojejunal anastomosis (Fig. 1, A). They failed to observe the occurrence of ulcer in the stripped portion of the jejunum. In four of ten dogs so operated ulcers were present just distal to the point where the muscle had not been de-

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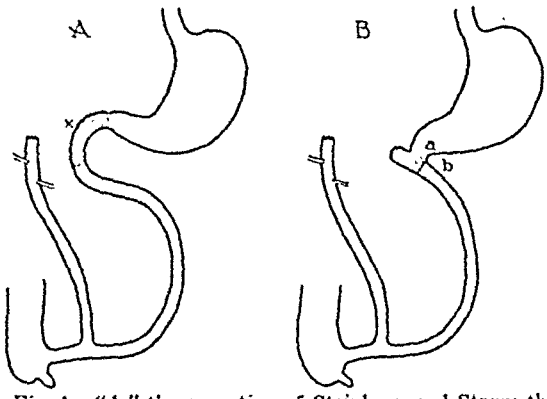


Fig. 1. "A," the operation of Steinberg and Starr; the portion marked "X" was stripped of three-fourths of its musculature. "B," our operation. Distance from "a" to "b," 3 cm.

nuded. This result, regardless of the fact that their ten animals survived the operation from only 7 to 76 days, was most interesting. We have slightly modified their operation and have extended their experiment to ascertain whether local muscular spasm in the jejunum is essential for the formation of jejunal ulcer.

METHOD

We performed the operation shown in Fig. 1, B, which differs from the Steinberg-Starr operation only in that we performed an end-to-side anastomosis. The longitudinal and circular musculature stripped readily and we were careful to remove the musculature surrounding three-fourths of the jejunum, leaving that adjacent to the mesentery intact. The stripping was done before the jejunum was incised longitudinally for the purpose of making the anastomosis. Further, our dogs were fed a special diet which we have shown previously (2) to maintain Mann-Williamson dogs in a better nutritional condition than the ordinary diet of meat, milk and bread. This diet consists essentially of cooked ground meat and cereal, milk, tomatoes and cod liver oil, corn syrup, raw ground liver and pancreas. This diet was fed twice daily in the amounts desired by each animal.

RESULTS

Control experiments: Twenty dogs were operated as shown in Fig. 1, B, except that the muscle was not denuded. They were fed the special diet. These dogs constituted the control group.

Ten of the animals survived from 9 to 17 weeks, only three dying with ulcer. Nine of the remainder survived from 20 to 58 weeks all having ulcer. One survived 82 weeks and did not develop ulcer. The average survival time of the 12 animals having ulcer was 26.7 weeks.

Experiments in which the jejunum was denuded of its musculature except for that one-fourth along the mysenteric border: Fifteen dogs were operated as shown in Fig. 1, B. They received the special diet. One of the fifteen developed a jejuno-duodenal anastomosis and survived for 76 weeks, and hence cannot be counted in this experimental series. Of the remaining 14 animals, thirteen died with ulcer at 10, 18, 14, 15, 26, 23, 36, 29, 78, 11, 34, 24, and 23 weeks. One animal which was anesthetized at 76 weeks did not have an ulcer. *The ulcer without an exception was located in the position of the jejunum stripped of its musculature or at the usual site,* and not where we expected it to be located, on the basis of the observations of Steinberg and Starr. The ulcers as a rule were large and very indurated. The base of the ulcer was usually not located at the site of the mesenteric border, and the ulcers perforated either on the anterior or posterior wall, although in some instances the adhesions were so marked as to render uncertain the exact location of the base of the ulcer in regard to the mesentery. The average survival time of the 13 animals having ulcer was 26 weeks.

DISCUSSION

It is reasonable to believe hypothetically that local muscular spasm might be an important predisposing factor for the development of ulcer. It is well known that spasm of the pyloric antrum may cause hemorrhages into the mucosa which result in hemorrhagic erosions. We had hoped that by using our special diet, which delays the onset of perforation and lethal hemorrhage, and by ruling out the factor of spasm by denuding the musculature, as in the experiments of Steinberg and Starr, ulcers would not develop. This hope was not realized. Neither was the time of onset of perforation and lethal hemorrhage significantly effected, because the average survival time of the control animals having ulcer was 26.7 weeks and that of the animals with a "denuded" jejunum was 26 weeks.

Our findings do not necessarily annul those of Steinberg and Starr, because we deliberately performed an end-to-side anastomosis and fed a diet which delays the onset of perforation and lethal hemorrhage. An end-to-side anastomosis would tend to reduce the factor of spasm because the jejunum is sectioned along the border opposite its mesentery, a point of obvious surgical import. A diet which retards the development of ulcer might give the local mechanisms in the jejunum time to compensate for and to reduce the factor of spasm. The animals of Steinberg and Starr lived a very short time as compared to the survival of our animals. Thus, local muscular spasm may be a factor which contributed to the more rapid development of an ulcer in its early stages. However, it is not an essential factor for the development of jejunal ulcer after gastrojejunostomy.

CONCLUSION

Local muscular spasm in the jejunum is not an essential factor for the development of jejunal ulcer after gastrojejunostomy.

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Glucose Tolerance as a Diagnostic Aid in Jaundice
III. Toxic Hepatitis*

By

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THE syndrome resulting from toxic changes in the liver has been variously described under such titles as Acute Catharrhal Jaundice, Toxic (Arsphenamine, Cinchophen) Jaundice, Acute Infectious Jaundice and Acute Yellow Atrophy. Such titles place undue emphasis upon the outstanding symptom of jaundice, rather than upon the marked underlying pathological lesion. A more comprehensive appreciation of this very important disease entity would be obtained by including all these cases under an appropriate common title, such as Toxic Hepatitis. This heading would therefore include all the so-called non-obstructive or non-surgical cases of jaundice.

Experimental observations on liver damage and repair constitute an important basis for comparison with corresponding clinical conditions and while not all these can be exactly duplicated in the experimental animal, the value of such observations nevertheless, cannot be overemphasized. There are three parts into which such experimental work may be divided. First: The accurate observation of the reaction in the liver, to the introduction of toxic substances. Second: The process of repair that follows this period of reaction. Third: Those factors which help or retard this reparative process.

From the clinical standpoint, there are two important facts which must be added to the above. First: The accurate means of detecting Toxic Hepatitis cases from other conditions associated with jaundice, and Second: The best method available to effectively treat the condition.

PATHOLOGY

Before describing the changes observed in the liver of experimental animals, following the administration of various toxins, it might be well to mention briefly some very important structural features of the liver itself. As is well known, the capillaries that are formed, after the union of the portal and hepatic terminals, run in part directly to the efferent or central vein of the liver lobule or to that of the adjoining one. (Fig. 1). It has been demonstrated that the portal vein and hepatic artery may be ligated separately without producing any serious effect, but if the smaller branches of the portal vein are occluded where the hepatic arterioles join them, the blood supply is cut off from the liver cells and they die. The bile capillaries are bounded on all sides by the liver cells forming the continuation of their lumen. The epithelium of these bile ducts is therefore of the same type as the liver cell but not so highly specialized. Furthermore, it must be emphasized that the elements which make up the liver tissue are not all equally resistant to toxic agents. The more highly specialized liver cells for example, are killed first by the action of toxins, leaving the less delicate bile-duct epithelium intact and capable of growth. The connective tissue frame-work and blood vessels are even more resistant to such toxic irritants.

The method commonly employed to produce diffuse injury of the hepatic parenchyma experimentally, with as little damage as possible to the other organs, has been by means of the administration of phosphorus and chloroform. The hepatic factor in such toxic processes seems quite outstanding and as Williamson and Mann (1) have emphasized, the liver is found to be the most seriously damaged organ both histologically and physiologically. Mosiman and Whipple (2) in their work along these lines showed that phosphorus attacks chiefly the cell protoplasm. Opie and Alford (3) found that the lesions produced by moderate phosphorus poisoning consist of fatty degenerative changes. In the early stages these lesions are confined to the centre of the lobules, while later they are most conspicuous near the portal spaces. In the severe types of poisoning with phosphorus, marked areas of coagulation necrosis are produced which have a tendency to involve the peripheral portion of the lobules. Whipple and Sperry (4) followed experimentally the lesions in various organs, caused by chloroform administration and gave an excellent histologic picture of the liver injury and repair.

In the laboratory animal, typical chloroform necrosis effects the centers of the liver lobules, and this damage can be definitely demonstrated six to ten hours after the administration of the drug. The dead areas usually appear hyaline and quite homogenous in from twenty-four to forty-eight hours. Wandering cells then make their appearance and aid the tissue fer-

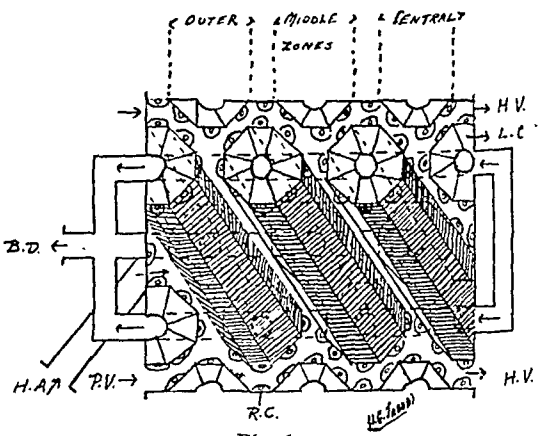


Fig. 1

Schematic drawing showing the structure of the liver lobule. H.A., Hepatic Artery. P.V., Portal Vein. B.D., Bile Ducts. H.V., Hepatic Vein. R.C., Reticuloendothelial Cells. L.C., Liver Cells, lining bile ducts.

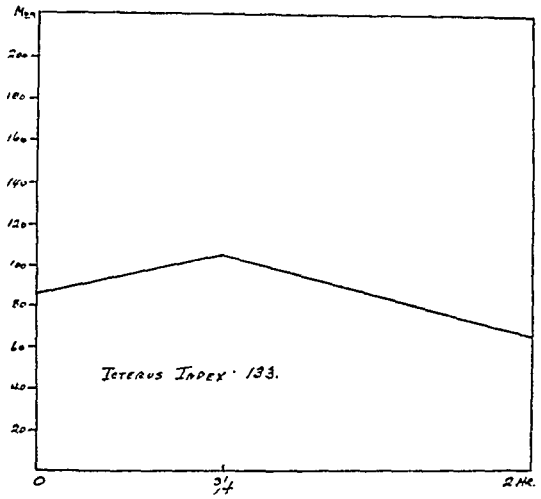
*From the Medical Service of Dr. A. L. Garbat.
†Associate Attending Physician, Lenox Hill Hospital.
Submitted November 25, 1936.

ments in removing the necrotic mass. In cases of recovery, this process occurs between the second and fifth days. During this process of dissolution, the neighboring intact liver cells begin to proliferate. Numerous mitotic figures are observed with the extension of cell strands into the stroma, which was recently filled with dead material. Even under the most favorable conditions, there is a period between the removal of the debris, and final repair, when a certain amount of unfilled stroma is to be seen surrounding the central vein. In an acute case of delayed chloroform poisoning, if death occurs within two or three days, the liver will be enlarged and yellow and many of the cells will show distention with fat globules. If death occurs in about a week or so, the liver will be much shrunken in size owing to the absorption of the cells which previously showed fatty distention. In both of these cases the liver cells must have undergone death from the toxic effects to which they had been exposed. It has been estimated that a liver necrosis involving practically 50% of all the liver parenchyma will be usually completely repaired in from seven to nine days, in the laboratory animal surviving such damage.

These above mentioned poisonous agents also impair the excretory power of the liver cells for removing bile from the blood, with the consequent increase in the concentration of the circulating bile pigments. This increase in circulating bile pigments usually results from some intrahepatic damage and functional derangement, whereby these bile pigments from the endothelial cells are unable to enter the polygonal cells and instead pass directly into the hepatic vein, and thence into the general circulation, where they continue to accumulate. A second mechanism that must be taken into consideration is the possibility of an excessive blood destruction occurring in the course of a toxic hepatitis. As a result of this, more bilirubin is formed in the reticulo-endothelial cells than can be absorbed by the liver cells. This excess of bile pigments passes directly into the hepatic veins and accumulates in the circulating blood. The degree of im-

Hist. No.	Age	Sex	On Admission		Diagnosis	Result	Post-Mortem Studies	Cholecystography with Tetraiodophenolphthalein
			Icterus Index	Fasting Blood Sugar				
39335	40	M.	40	74 mgm. 100 c.c.	Catarrhal Jaundice	Cured		Not Performed
44071	50	F.	110	50 mgm.	Acute Yellow Atrophy	Died	Showed Acute Yellow Atrophy of Liver	Not Performed
44210	42	F.	105	82 mgm	Toxic Hepatitis	Cured		Visualized at Icterus of 58
37017	55	M.	20	80 mgm.	Catarrhal Jaundice	Cured		Visualized
45631	20	M.	44	86 mgm.	Catarrhal Jaundice	Cured		Not Performed
41792	59	M.	62	80 mgm.	Catarrhal Jaundice	Cured		Not Performed
41947	40	M.	133	86 mgm.	Catarrhal Jaundice	Cured		Visualized
41814	30	M.	62.5	80 mgm	Catarrhal Jaundice	Cured		Visualized
41027	41	M.	166	75 mgm	Catarrhal Jaundice	Cured		Not Performed
34277	52	M.	116	87 mgm	Acute Yellow Atrophy	Operation Died	Acute Yellow Atrophy No Carcinoma of Pancreas	Not Performed
24284	27	M.	250	84 mgm	Toxic Hepatitis	Operation Recovered		Not Performed
19576	21	M.	31	90 mgm.	Catarrhal Jaundice	Cured		Visualized
26704	59	M.	137	96 mgm	Acute Yellow Atrophy	Died	Acute Yellow Atrophy	Not Performed
17366	43	M.	140	92 mgm	Toxic Hepatitis	Cured		Not Performed
35869	42	M.	130	84 mgm.	Catarrhal Jaundice	Cured		Not Performed
36154	54	M.	13.5	80 mgm.	Toxic Hepatitis	Cured		Not Performed
12887	22	M.	160	90 mgm	Toxic Hepatitis	Operation Recovered		Not Performed
25094	48	M.	38	80 mgm.	Acute Yellow Atrophy	Died	Not Obtained	Not Performed
16485	39	M.	37.7	99 mgm	Acute Yellow Atrophy	Operation Died	Acute Yellow Atrophy	Not Performed
36566	42	M.	200	84 mgm	Acute Yellow Atrophy	Died	Acute Yellow Atrophy	Not Performed
34656	27	M.	96	88 mgm.	Catarrhal Jaundice	Cured		Not Performed
36727	21	F.	135	86 mgm.	Catarrhal Jaundice	Cured		Visualized at Icterus of 66
30209	26	F.	110	84 mgm	Catarrhal Jaundice	Cured		No Visualization
15743	51	F.	65	90 mgm.	Catarrhal Jaundice	Cured		Visualized
52139	34	M.	237	81 mgm.	Catarrhal Jaundice	Cured		Visualized

CHART I



Graph 1

Case 41847. Age 40. Sex, Male. Gall bladder visualized at icterus of 66. Sugar tolerance curve.

pairment in this function of the liver can be definitely determined by means of the icterus index (5).

HEPATIC GLYCOGEN AND BLOOD SUGAR

The presence of glycogen and glucose in the liver cells, seems to increase their power of resistance to all toxic agents. This assumption has been definitely confirmed by the work of Whipple and Sperry (4) and Davis (6). Graham (7) found that the resistance of pups to late chloroform poisoning is due to their increased hepatic glycogen. This resistance could be destroyed by starving the pups. On the other hand adult dogs were found to have a lessened susceptibility to poisons after a period of high carbohydrate feeding. Likewise Davis and Whipple (8) found that starved animals are very susceptible to liver injury from chloroform. Adequate sugar administration or the intake of diets rich in carbohydrates for several days preceding the chloroform anesthesia, exerts a marked protective action against liver injury. They therefore suggested this as a method of treatment, in cases of toxic liver damage.

In patients with hepatic disease, Althausen and Thoenes (9) noted that after receiving 20 units of insulin and 50 gm. of dextrose orally there was usually observed an initial rise in the blood sugar followed by an abrupt decline. In some cases, no initial rise was observed, but an uninterrupted diminution of the blood sugar level occurred. Both these type curves ended in marked hypoglycemia. In animals with experimentally induced liver damage, these investigators (10) found that the first functional deficiency of the liver to be observed following toxic injury, was a failure on the part of this organ to maintain the normal blood sugar level, and in the last stages of poisoning, blood sugar curves ending in hypoglycemia were rather typical, after the modified dextrose tolerance test. Unfortunately, however, no icterus index determinations were made in any of these animal experiments. Meulengracht (11) likewise reports that in cases of acute hepatitis, accompanied by various degrees of icterus, the fasting blood sugar value was found to be below the normal figure. In three cases of severe hepatitis terminating in death with features of acute yellow atrophy, he found very low fasting blood sugars, the lowest being 33 mgm. per 100 c.c. of blood.

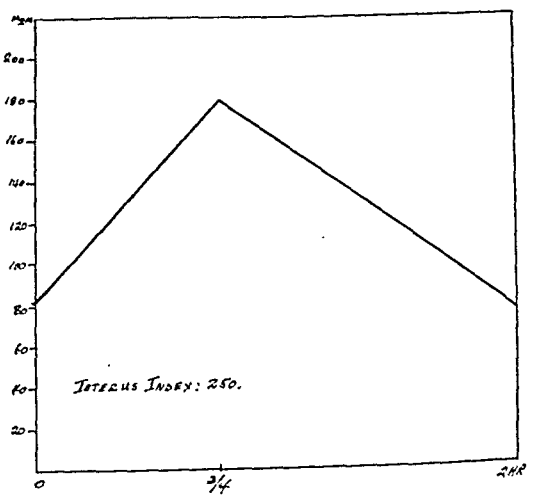
In a previous communication (12) I reported a group of jaundice patients, showing their response to the administration of glucose by means of the ordinary sugar tolerance test. The toxic cases showed a fairly typical reaction whereby the blood sugar at the end of the two hour period always returned to normal levels, and showed very little increase in the blood sugar in spite of tremendous doses of glucose administered. This response was not obtained in cases of obstructive jaundice.

BILE AND GLYCOGEN FORMATION IN THE LIVER

Very little work has been done on the exact relationship existing between the glycogen formation and the bile formation function of the liver. Forsgren's (13) observations may be mentioned in this connection as warranting further corroborative investigation. He concluded from his experimental work on rabbits, that an antagonism exists in the liver cells between bile formation and glycogen formation. These two processes appear unable under normal conditions, to simultaneously attain a maximum. He also found that within the periphery of the lobule, the liver cells are more often engaged in the formation of bile, while within the central zones they are more engaged in the formation of glycogen. Both these processes of bile and glycogen formation were found to proceed in definite periodic cycles during the twenty-four hour period. Such observations are of extreme importance in their bearing on the behavior of glucose administered in the presence of jaundice.

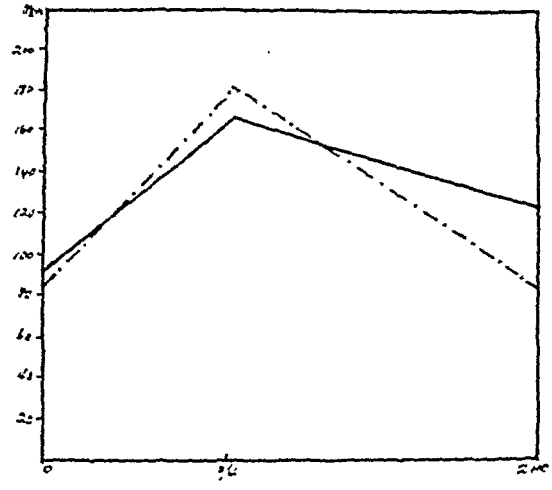
GALL BLADDER VISUALIZATION IN TOXIC JAUNDICE

The use of tetraiodophenolphthalein as a means of testing the physiological capacity of the excretory function of the liver in the presence of jaundice has not been sufficiently stressed. We feel that this procedure has not received the attention that it deserves



Graph 2

Case 44210. Age 42. Sex, Female. Gall bladder visualized at icterus of 58. Sugar tolerance curve.



Graph 3

Case A. D. History No. 44210. Age 42 years. ——— Date 1 31 35. Icterus Index 105. —.—.— Date 3 12 35. Icterus Index 42. Sugar tolerance curves.

as a diagnostic aid in jaundice. Considerable aloofness has been shown to the employment of gall bladder visualization in the presence of jaundice. This attitude probably originated with the report of early studies on the intravenous method of administration of the dye when harmful toxic reactions were reported, due to the impurities present when the dye was first introduced and also to the intravenous method of administration. In 1930, Rudisill (14) reported the intravenous use of the dye for gall bladder visualization in a series of eight cases of infectious jaundice, without any harmful effects. In seven of these cases he was successful in obtaining visualization. The exact degree of icterus in these cases is not given. Foley (15) reported a series of 29 cases of jaundice in whom gall bladder visualization by the oral method was performed. Of this entire group 16 were cases of toxic or non-obstructive jaundice and 13 were surgical or obstructive jaundice cases. In the obstructive jaundice cases no visualization was obtained. In the toxic group 11 of them showed a gall bladder shadow after the oral administration of the dye. The highest icterus index at which such visualization was obtained in this group of toxic cases was 90. Foley further states that he has been in the habit of doing cholecystography in cases of jaundice with the understanding that a negative shadow is of no significance either way. A positive shadow, however, in the presence of jaundice indicates the normal functioning of the extra-hepatic bile ducts and therefore establishes the cause of the icterus as due to some intra-hepatic pathology.

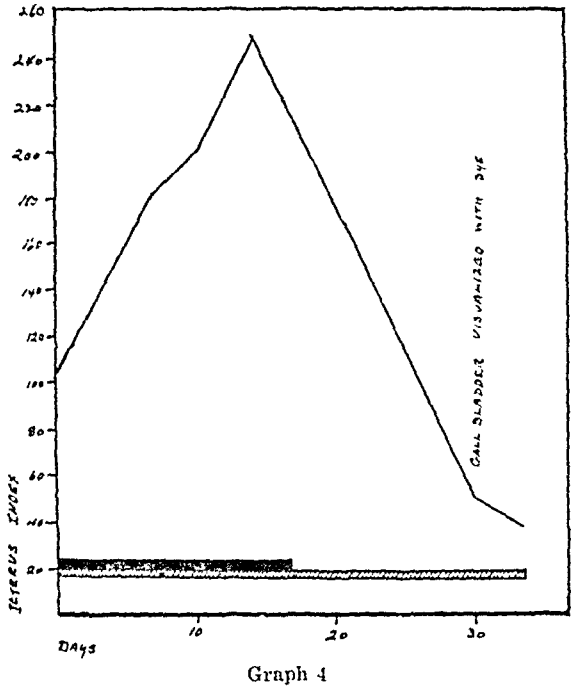
Foley's observations agree with our findings (12) where we obtained gall bladder visualization by means of the oral method in 7 out of 8 cases of toxic jaundice. The highest icterus index at which successful visualization was obtained in these 7 cases was 66.

PROCEDURE

The fasting blood sugar and icterus index determinations are made on all jaundice patients, shortly after admission to the hospital. A sugar tolerance test, using 100 grams of glucose is performed. While half hourly determinations of the blood sugar may be made, we have found that the 45 minute and 2 hour observations furnished the necessary information. Cases that show a return of the blood sugar to normal at the end of the two hour period with blood sugar curves corresponding to those shown in Graph 1 or Graph 2, receive 250 Gm. of glucose orally and a continuous intravenous drip of 10 to 15% glucose solution. Icterus index determinations are made every other day. After about 7 or 8 days of this intensive glucose therapy, gall bladder visualization by means of the oral method is attempted.

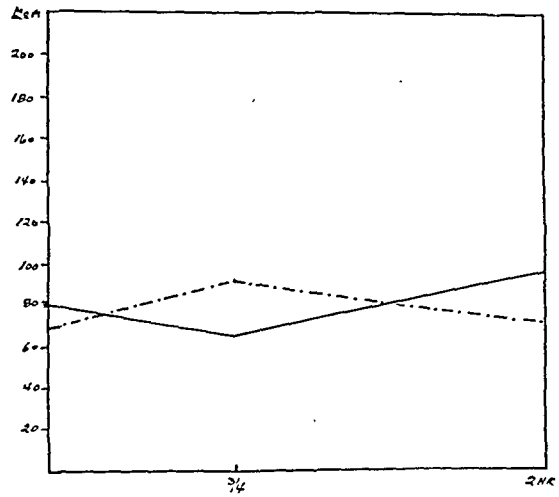
OBSERVATIONS

Our present report is based upon a study of twenty-five cases. There are 20 males and 5 females in the group (Chart 1). The ages vary from 20 to 59 years. The icterus index varies from 13.5 to 250. All the cases responded to the glucose tolerance test in one of the two following ways: The flat curve, similar to that shown in Graph 1, where the rise in the blood sugar is very slight throughout the period following the intake of the glucose. The second type reveals a low fasting blood sugar followed by an early high rise and a subsequent fall to the normal level at the end of the 2 hour period. An example of this type of curve is shown in Graph 2. The first type of curve is obtained in those cases of toxic hepatitis where the toxicity is quite severe and where the icterus index is high, while the second type which is the usual normal sugar tolerance curve, is seen in cases where the icterus index is below 40 and where not much toxicity is present. The important feature of both those curves is that the blood sugar at the end of the two hour period returns to the normal level. The fasting blood sugar level is rarely elevated in these cases and seems to bear a direct relationship to the severity and duration of the toxic process. As this process increases in



Graph 4

Case A. D. History No. 44210. Age 42 years. Icterus index curve.



Graph 5

Case K. C. History No. 52139. Age 34 years. ——— Date 5/6/36. Icterus Index 227. —.—.— Date 5/18/36. Icterus Index 33. Sugar tolerance curves.

severity, the fasting blood sugar values become lower and some of our lowest figures are noted in the fatal cases that develop into acute yellow atrophy. The lowest fasting blood sugar for the group is 50 milligrams per 100 cubic centimeters of blood and highest 99 milligrams per 100 cubic centimeters of blood, with an average of 78 milligrams per 100 cubic centimeters of blood. In 9 of the cases in this group, gall bladder visualization was attempted and was successful in 8 of them. The highest icterus index at which successful gall bladder visualization has been obtained in these 8 cases is 66. The icterus index in the unsuccessful case is 100. There are six deaths in the group. In five of these cases post-mortem examination was made. Four of the cases were operated upon as the possibility of an obstructive type of jaundice was considered as very likely. Two of these operative cases resulted in death. One case was diagnosed by the operating surgeon as an inoperable carcinoma of the head of the pancreas. This patient died and post-mortem examination failed to reveal the carcinoma but showed the jaundice to be due to an Acute Yellow Atrophy.

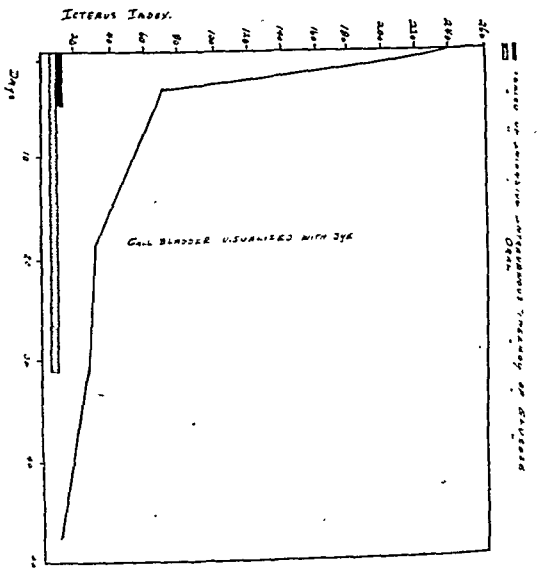
We have selected four cases for detailed report, in order to point out some of the more important features of this group. Of these four cases two made complete recoveries and in the other two where death occurred complete post-mortem studies have enabled us to correlate such findings with our clinical and laboratory data.

CASE REPORTS

Case 1: A. D. Hist. No. 44210. Age 42 years, was admitted to the hospital on Jan. 30, 1935, complaining of jaundice and abdominal distress of several days duration. The patient had only recently, 12/14/34, been operated upon in the Gynecological Service of the hospital for a bilateral tubo-ovarian abscess. She had had a rather stormy convalescence, and was discharged on 1/13/35 in good condition. For the first ten days of her stay at home the patient continued to feel well. On the tenth day, however, she noticed that her eyes were yellow, and that she had a bad taste in her mouth. Her appetite was fair. There was some abdominal distress and slight pain in the right upper quadrant. There was no history of any upper respiratory infection. The only other significant feature in her past history was the fact that one year previously she had received quite a number of intramuscular injections for some "blood condition."

Physical examination on admission reveals a well developed and well nourished female who is markedly jaundiced. She has considerable dental caries and her mouth hygiene is quite bad. The chest is emphysematous in shape, no abnormal findings are present. The heart is negative. The abdomen is distended and the liver felt about one finger breadth below the costal margin. Spleen is not felt. Knee jerks present. Temperature is 99.6. Pulse 70. Respiration 22. The icterus index on admission is 105. The glucose tolerance test performed on 1/31/35 shows fasting blood sugar of 86 mgm. per 100 c.c. of blood. Forty-five minute specimen is 166 mgm. and the two hour specimen, 122 mgm. per 100 c.c. of blood. In other words, it shows a typical non-obstructive or toxic curve (Graph 3). The patient is therefore immediately placed upon the high carbohydrate regime with glucose therapy intravenously, and also by means of the rectal drip. On Feb. 3, 1935, three days after admission, the patient shows a marked rise in the temperature to 102.2 and appears very toxic. On 2/6/35 the icterus index is 181 and the patient complains of a good deal of nausea and vomiting and appears much more toxic and considerably worse than at the time of admission. On 2/9/35 the icterus index is 200 and by 2/15/35 it is 250 (Graph 4).

Several of the physicians in attendance are rather inclined to the idea that this is perhaps a case of common duct obstruction that should be operated upon. We are quite determined, however, to continue with the therapy above outlined especially after a repeat sugar tolerance test again shows a non-obstructive curve similar to the first one (Graph 3). The flat plate of the abdomen is negative. On 2/21/35 the patient shows a marked improvement and the icterus index is down to 166. This improvement on the part of the patient continues and so by 3/4/35 her icterus index is 58. At this point an attempt is made at the visualization of the gall bladder by the oral method (Fig. 2). An excellent gall bladder shadow is obtained in this case with an icterus index of 58. On March 12, 1935, the sugar tolerance test is repeated and



Graph 6

Case K. C. History No. 52139. Age 34 years. Sex, Male. Icterus index curve.

still found to be of the non-obstructive type (Graph 3). The patient left the hospital completely cured.

Case 2: K. C. Hist. No. 52139. Age 34 years, was admitted to the hospital on May 6, 1936, with the complaints of jaundice and severe itching of four weeks duration. Patient related that about five weeks previously he had been on a drinking spree which lasted all night. Following this he developed an upper respiratory infection which lasted for about 4 to 5 days. He then began to have nausea, vomiting, and gaseous distention for about two or three days. By this time he was definitely icteric and this together with his pruritis have been increasing since then. The stools were clay colored, and the urine dark red in color. There was a loss of 24 pounds in weight during the five week period. There was no history of drug ingestion, or of any intravenous therapy. The patient is employed as a salesman. There is nothing of any significance in his past or personal histories.

Physical examination reveals a well developed and well nourished young man who is markedly jaundiced. The temperature is 99.2, pulse 90, respiration 20 and blood pressure 136/80. There is marked evidence of scratching over the entire body. Patient is mentally alert. Mouth and throat are negative. The heart and lungs are negative. The abdomen shows the liver palpable, about three fingers breadth below the costal margin. Spleen is not palpable. No tenderness and no edema are present. Reflexes are active. Flat plate of the abdomen fails to reveal any evidence of calculus. The icterus index on admission is 227 and the glucose tolerance test shows fasting blood sugar of 81 mgm. per 100 c.c. of blood and 66 mgm. and 97 mgm. at the 45 minute and 2 hour period after the ingestion of the 100 gm. of glucose (Graph 5). The Wassermann test is negative. No diagnostic aid is obtained from the galactose tolerance test or the determination of cholesterol or cholesterol esters. The patient is immediately given high carbohydrate intake and 15% glucose intravenously in the form of a continuous drip with the arm put up in a supporting cast and a cannula inserted into the vein. The patient receives about 1500 c.c. during the 24 hour period in this way. On the fourth day of this intensive therapy, the icterus index is down to 71. On 5/18/36 the icterus index is further reduced to 66, and on 5/23/36 it is down to 33 (Graph 6). At this time the sugar tolerance test is repeated and shows 71 mgm., 92 mgm. and 74 mgm. for the fasting, 45 minute and 2 hour specimens respectively (Graph 5). The oral Graham test is performed at about this time with an excellent shadow obtained (Fig. 3). The patient is discharged from the hospital on June 26, 1936, with his icterus index down from 227 to 10 (Graph 6).

At a follow up clinic on Oct. 25, 1936, the patient reported that he was feeling perfectly well.

Case 3: (H. N. 44071). Female, 50 years old, who was admitted to the hospital on Nov. 7, 1934, with the history that six weeks previously she consulted a physician because of painful and swollen joints. These pains had been increasing in severity since their onset one year ago. Her doctor gave her 18 intravenous injections of some salicylate preparation, supposedly manufactured by some drug manufacturer and also a certain preparation of his own. The exact nature of these injections could not be definitely determined. Three weeks prior to admission she developed nausea, vomiting and jaundice. She has gradually become weaker and three days before admission she developed a temperature and gave evidence of some toxicity, as manifested by mental confusion, and nervousness.

The only other significant feature in her history was the fact that five years previously she underwent a series of injections for varicose veins, following which she became quite ill, and developed jaundice. These symptoms cleared, however, at the end of two weeks.

Examination of the patient reveals a rather obese middle aged white female who is very restless and somewhat irrational. Pulse is 124. Respiration 18. Temperature 101.6. Marked jaundice is noted of the skin and sclera. Lungs and heart do not show any abnormal findings. The abdomen is distended and the liver palpable two finger breadths below the costal margin. The spleen is not felt, the icterus index is 110 and the sugar tolerance curve reveals, fasting specimen of 50 mgm. blood sugar per 100 c.c. of blood. The 45 minute specimen is 88 mgm. and the two hour specimen 84 mgm. This curve is the flat type, similar to that shown in Graph 1. The diagnosis of a severe toxic jaundice is therefore made and intensive intravenous glucose therapy instituted. The patient's condition becomes progressively worse, and death occurs only three days after admission to the hospital. Post-mortem examination was obtained, and we shall of course limit our findings to the pathology of the liver. This is found greatly diminished in size, greenish in color, with intermittant yellow and hemorrhagic areas. The gall bladder is distended with approximately a dozen large facetted stones. No stones are found in the common or cystic duct. The liver, on removal, has a jelly-like consistency and on section shows the same yellowish and hemorrhagic areas throughout its entire substance. Microscopically there is noted a marked degree of granular degeneration involving practically all of the liver cells. The liver architecture and cells are completely destroyed, and necrotic. A diffuse leucotyic infiltration is noticed throughout.

Case 4: (H. N. 36566). Male, 42 years old, who was admitted to the hospital with the history that 2 weeks previously, he had a sore-throat, which lasted only for about 2 to 3 days. Following this the patient felt very weak and languid and had marked anorexia. Shortly after this a friend of the patient's noticed that he was jaundiced and this continued to increase in intensity up to the time of admission. There was some slight epigastric discomfort especially on walking. At about the time that the jaundice was discovered the patient noticed that his stools were clay colored and his urine dark reddish in color. There was no history of a previous attack of jaundice. There was nothing significant in the past history. The patient was married 12 years, wife was living and well. There were no children. On admission to the hospital the patient shows a pulse of 76, respiration 20 and temperature 99.4. He is a well developed and well nourished white male, who does not appear acutely ill. He is markedly icteric. There is a marked pyorrhoea of the gums and three unextracted roots are present in the upper jaw. These show considerable infection around them. The tonsils are cryptic and the pharynx markedly reddened. There is an enlarged gland present at the angle of the left jaw. The lungs are negative. The heart is slightly enlarged, with a soft systolic murmur present over the precordium. The abdomen is soft. The spleen is slightly enlarged to precussion and the liver is felt about two finger breadths below the costal margin. The blood Wassermann reaction is negative. X-ray confirms the presence of the unextracted roots, with apical infection present in the upper left lateral and bicuspid and upper right lateral roots. The icterus index is 87.5 and the glucose tolerance curve shows a fasting blood sugar of 84 mgm. per 100 c.c. of blood. The 45 minute and 2 hour specimens are 92 mgm. and 74 mgm. respectively.

Intensive glucose therapy orally and intravenously is instituted but in spite of this on Feb. 13, 1933, five days after admission, the icterus index has increased to 96, and the patient is beginning to have a septic temperature, with a markedly reddened throat. A blood culture taken on this day, shows a positive hemolytic streptococcus growth. The patient continues to appear very toxic and drowsy and on Feb. 20, 1933, the icterus index is 200. The intensive

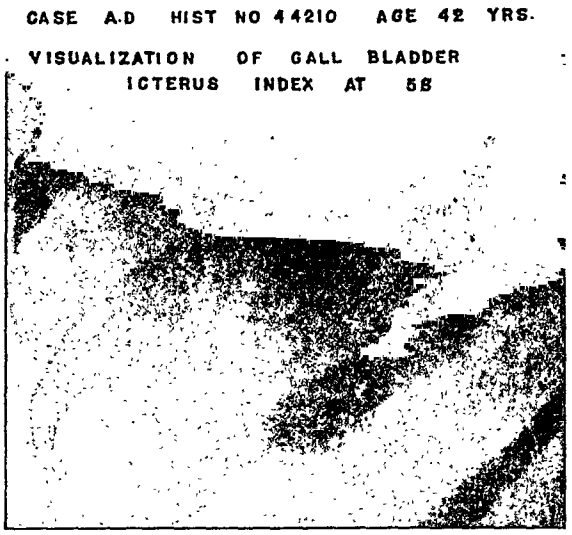


Fig. 2

therapy however is still continued. Two days later the temperature is normal, and the icterus index on Feb. 24, 1933, is down to 110. The patient appears much brighter and not at all toxic. A check on the blood culture on Feb. 16, 1933, reveals a sterile result. Feb. 26, 1933, the patient develops a large area of erythema on the back with a new rise in temperature and marked toxicity. On March 21, the icterus index is up again to 200 and the glucose tolerance test shows a fasting blood sugar of 74 mgm. and a 45 minute and 2 hour specimen of 78 mgm. and 60 mgm. respectively. The patient continues to grow steadily worse in spite of intensive intravenous and oral glucose therapy. The icterus index on March 7 is still 200 and on March 12 is the same. The sugar tolerance test on this day shows a fasting blood sugar of only 66 mgm. and a 45 minute and 2 hour specimen of 68 mgm. and 55 mgm. respectively. The patient continues to grow worse and expires.

Post-mortem: Examination reveals a small liver with scattered areas of greenish yellow markings throughout the organ. Microscopically there is seen a large number of liver cells completely destroyed and an apparent as well as a real cirrhosis due to the collapse of the stroma and an increase in the fibrous tissue. Throughout the sections there are found degenerating liver cells, serum, red blood corpuscles and inflammatory cells of all types. These inflammatory cells often form small collections in the stroma and the remaining liver cells.

DISCUSSION

Case 1 illustrates very decidedly the advantage of relying upon the glucose tolerance test, even in view of the fact that the patient's icterus continued to mount after admission to the hospital and after the intensive glucose therapy had been instituted. Some men even felt that surgical intervention should be undertaken. The galactose tolerance test, blood cholesterol and cholesterol esther determinations were of no value here. The flat plate of the abdomen was negative. It was really the intensive glucose therapy, intravenously, orally and by rectal drip that caused the marked improvement in this case. The visualization of the gall bladder was obtained with an icterus index of 58. This agrees with the results of Rudisill and Foley with similar experiences in cases of toxic jaundice.

Case 2 shows quite dramatically the excellent response obtained in these toxic hepatitis cases to the intensive administration of glucose intravenously. This patient was kept in bed and a cast made in order to immobilize his arm which contained a cannula sutured into the vein. The solution used was 15% glucose in Ringer's solution and of this the patient received between 1000 and 1500 c.c. during the 24 hour period, as an intravenous drip. How extremely effective this method of treatment is can be judged by the marked reduction of the icterus index from 227 on May 7, 1936, to 71 on May 14, 1936. Such results certainly warrant the advocating of this intensive method of glucose administration in all these toxic hepatitis cases with marked jaundice.

Case 3 shows a rather severe toxic hepatitis caused apparently by some preparation used intravenously for the relief of arthritic pains, probably cinchophen. The fact that this patient developed jaundice five years previously, following injections for varicose veins should have suggested to the attending physician, the susceptibility of the liver to damage, from the intravenous use of cinchophen. The sugar tolerance test on admission showed a very low fasting value of 50 mgm. per 100 c.c. of blood. The 45 minute and 2 hour specimens of 88 mgm. and 84 mgm. respectively likewise showed very little rise to the ingestion of the glucose. This curve is of the flat variety which in our experience denotes a toxic involvement of the liver of rather marked severity. The intensive glucose administration intravenously was of no help in this rather pronounced and advanced toxic lesion. It is of interest to note that the gall bladder contained about a dozen facetted stones. Mention is made of this fact because of the incorrect inference that could be drawn by a surgeon, operating upon a patient similar to this one and finding stones in the gall bladder. The natural conclusion would be to consider the case as one of obstructive jaundice. The glucose tolerance test appears to have given the more correct understanding of the underlying lesion.

Case 4 shows the course of a severe infection resulting in serious liver damage. The patient showed a typical non-obstructive sugar tolerance curve of the flat type. Under intensive oral and intravenous glucose therapy the patient began to show signs of improvement as evidenced by the drop in the temperature and also a reduction in the icterus index from 200 to 110. A few days later, however, a second infection (erysipelas) set in with a return of the icterus index to 200 and accompanied by a return of the marked toxic symptoms. This infection was apparently more than could be handled by this patient and he finally succumbed to it. The fasting blood sugars of the two subsequent sugar tolerance curves was 74 mgm. and 66 mgm. respectively. This decrease in the fasting blood sugar has been recognized as a bad prognostic sign in these severe toxic lesions of the liver.

From the available experimental and clinical data that has been presented one would certainly be justified in making the statement that glucose plays a very important role in toxic hepatitis. An attempt has been made here to utilize this reaction to glucose on the part of such patients, both from the diagnostic and therapeutic view points.

Various methods have been advocated for the differentiation of the so-called toxic from the obstructive

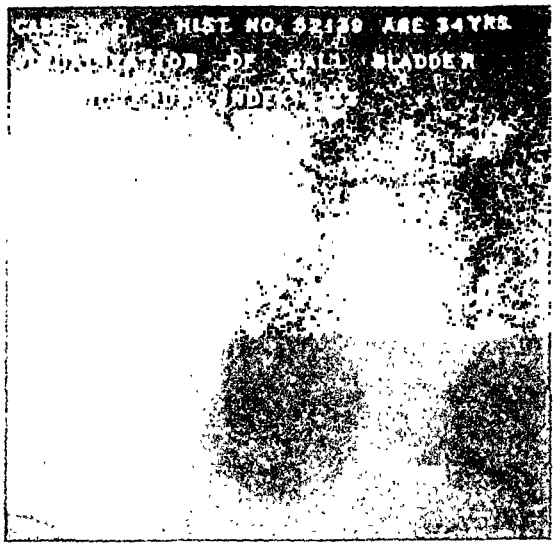


Fig. 3

cases of jaundice. These have included such determinations as the van den Berg, the galactose tolerance test, the study of uribilin, plasma cholesterol, cholesterol esters, etc. All of these, however, have been found wanting because of the variability in the results obtained. Thus in 1906, Bauer (16) attempted to utilize his galactose tolerance test as a means of identifying cases of toxic jaundice. Subsequent work has shown, however, that this claim is entirely too enthusiastic and oftimes misleading. Banks, Sprague and Snell (17) in a careful evaluation of this procedure arrived at the conclusion that it cannot be relied upon solely as a diagnostic procedure to distinguish between toxic and obstructive jaundice. In a previous communication (12) we have shown that such cases of toxic hepatitis with jaundice show certain characteristic blood sugar responses to the oral administration of glucose and that many of these cases that were previously subjected to operative procedures could be spared this additional strain if proper classification of these cases is made. Without entering into any theoretical explanation as to the exact mechanism which is involved in this reaction, we merely wish to stress our observation that whenever a case of jaundice gives a sugar tolerance curve, similar to that of Graph 1 or 2, the underlying pathology of the jaundice is due to toxic or non-obstructive causes and the intensive administration of glucose both orally and intravenously is definitely indicated. In such cases there should be no hesitancy to cut down on the vein in order to insure a regular and constant flow of glucose into the circulation. The arm should be immobilized by the application of a cast. The fact that such cases continue to show an increase in the icterus index even after the glucose therapy has been instituted for several days often causes unnecessary uneasiness and haste in advocating an exploratory operation. Such hasty action should be avoided and will help materially to diminish the mortality rate in the condition.

Our post-mortem studies have also brought out the fact quite clearly that the presence of calculi in the gall bladder is no definite proof that the existing jaundice is due to mechanical obstruction for we have on several occasions found calculi in the gall bladder and still definite pathological findings in the liver indicating an acute yellow atrophy, as the cause of the condition.

It also appears that the excretion of tetraiodophenolphthalein is closely associated with glucose assimulation in the body. Thus Antonucci (18) has shown that the gall bladder may be visualized more rapidly when large doses of glucose are administered. Stewart and Illick (19) also found that the excretion of dye by the liver is facilitated by the simultaneous administration of sugar, and have utilized this principle by giving sugar by mouth along with the oral administration of the dye to obtain a maximum of liver excretion.

Such visualization of the gall bladder in the presence of jaundice has in our experience been present only in the cases of toxic jaundice. We therefore agree with the opinion expressed by Foley, that the absence of a shadow is of no value at all, but the presence of one confirms the existence of a non-obstructive jaundice.

SUMMARY AND CONCLUSIONS

1. Toxic hepatitis cases show a marked capacity for utilizing large amounts of glucose, regardless of the mode of administration.

2. These cases react in a fairly characteristic manner to the usual glucose tolerance test by showing blood sugar curves similar to those seen in Graph 1 or Graph 2, the characteristic feature of which is a return to the normal level at the end of the two hour period.

3. As a rule, the more severe cases show a reaction similar to that seen in Graph 1.

4. No definite relationship has been found to exist between the degree of icterus and the severity of the toxic process.

5. Surgical intervention should be avoided in those cases of jaundice which show either of the above two sugar tolerance curves.

6. Intensive intravenous glucose therapy, by means of the continuous drip method, with cannula sutured into vein and arm immobilized in a cast, gives the most marked and most immediate beneficial results in these cases.

7. Visualization of the gall bladder with the oral administration of the dye was successful in seven out of eight of these cases in which it was attempted. The highest icterus index at which such visualization occurred was 66.

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The Mechanism of Milk Clotting*

I. Role of Milk Components in Coagulation

By

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MILK is a heterogeneous system of relatively simple composition. Its state determines the mode of utilization by the body and its content the nutrient value; the one is physical and variant, and the other, chemical and relatively constant. In pediatrics we are more concerned with the behavior of milk than with its content. And knowledge of the mechanism of clotting is invaluable in modifying milk for digestive tolerance.

The apparent simplicity of milk clotting is needlessly confused by terminology and theory. We have approached the problem by studying synthetic solutions containing the clotting compounds that are necessary and sufficient. By varying one factor, be it chemical or physical, the changes during clotting have thrown light on the mechanism. These physicochemical studies parallel those previously made of blood clotting (1). Indeed the clotting of milk with rennin is similar to that of blood with thrombin in the presence of calcium ions.

Three constituents of milk form the clot — caseinate, phosphate, calcium. They compose but two per cent of milk and yet play so determining a role. Their chemical relation in fluid milk is given in Figure 1 where concentrations are expressed in terms of normalities to indicate equivalent combining powers of basic and acid-forming elements to form the salts of milk. In cow's milk all of the calcium is combined with casein as calcium caseinate and with most of the phosphoric acid as calcium phosphates. The three clotting constituents of milk form the largest molecular aggregates.

Milk may be coagulated by rennin, acid, heat or by a combination of them. The resulting clot differs with each method although casein in some form is the end product. Rennet coagulation is most involved. Hammersten (2) first demonstrated that rennin hydrolyzes some of the casein to paracasein. Schmidt-Nielson (3) recovered this fraction with proteose-like properties as distinct from the original casein. Linderstrom-Lang (4) showed that rennet splits casein, a complex of several substances, into its constituents, the flocculating fraction being paracasein. Upon addition of soluble calcium salts Hammersten (5) obtained a flaky precipitate with paracasein and a tough clot when calcium phosphate precipitated with the paracasein. The rennet clotting of milk is thus a two-stage process, first considered physical by Lindet and Ammann (6), colloidal by Kreidl and Neumann (7), adsorption by Mellanby (8), chemical by Bosworth (9) and physicochemical by Palmer and Richardson (10). We have studied the changes occurring during coagulation by applying the technique developed for following the course of blood clotting.

PREPARATION OF COMPONENTS OF CLOTTING SYSTEM

Casein was prepared as a base-free protein by the method of L. L. Van Slyke (11) which yielded a snow white powder readily dispersed in alkali.

Calcium caseinate solution was prepared by dissolving 15 gms. of pure cesein in sufficient lime water to give a pH 8.0. The solution was neutralized to pH 6.5 with 1% H_3PO_4, 2.5 c.c. 0.1 M $CaCl_2$ added and then diluted to 300 c.c. It gave a 5% artificial milk of pH 6.5 preserved with 0.1 c.c. octyl alcohol and 0.1 c.c. toluol.

TABLE I

Relation between clotting time and volume variation

Clotting System at 37° C. 5% Calcium Caseinate 25 c.c. 1% Rennin 0.2 c.c.		
Vol. Increase	0.2 N Ca Cl_2	Clotting Time
x 1	5 c.c.	160"
x 2	10 c.c.	165"
x 3	15 c.c.	168"
x 4	20 c.c.	162"
x 5	25 c.c.	165"

Paracasein was prepared as a modified base-free casein from skim milk warmed and passed through a

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TABLE II

Relation between clotting time of milk and moderate dilution

5% Calcium Caseinate 25 c.c.: 0.2 N $CaCl_2$ 5 c.c.: 1% Rennin 0.2 c.c.									
Milk	100	90	80	70	60	50	40	30	20
Water	0	10	20	30	40	50	60	70	80
Clotting Time	200"	210"	220"	250"	310"	370"	1110"	2500"	5000"
Clotting Power	100	96	91	80	65	35	18	8	4

supercentrifuge. The milk was then dialyzed free from soluble salts in collodion bags, diluted with an equal volume of H_2O and held at 30° C. for a half hour in presence of rennet solution. On cooling to 20° C.

TABLE III

Relation between clotting time of milk and extreme dilution

Clotting System at 37° C. 5% Calcium Caseinate 25 c.c. 0.2 N $CaCl_2$ 5 c.c. 1% Rennin 0.2 c.c.				
Water Added	Clotting Time	Curd	log v	log t
0 c.c.	3 min.	Tough		
2	5			
4	20	Gelatinous		
6	31			
8	38	Soft	0	0.58
10	46		1	1.67
100	210	Flocculant	2	2.32
1,000	260		3	2.42
10,000	240	Gritty	4	2.38

paracasein was isolated and purified by the method used for casein. The yield was a fine white powder readily dispersed in alkali.

Rennin was obtained from rennet extract prepared

TABLE IV

Relation of Rennet concentration to clotting time

Clotting System at 37° C. 5% Calcium Caseinate 25 c.c. 0.2 N $CaCl_2$ 5 c.c.	
1% Rennet	Clotting Time
0.05	650 sec.
0.1	290
0.2	180
0.4	95
0.6	70
0.8	50
1.0	40

fresh from calves' stomachs preserved with NaCl, boric acid and thymol, dialyzed free from Cl and filtered. One c.c. of a 1% solution gave clot in 15 minutes added to 100 c.c. cow's milk at 40° C.

Buffer Solution was prepared by adding N/15 phosphate solutions according to Sorensen. A mixture of 4 volumes of the primary phosphate and 1 volume of secondary phosphate gave pH 6.3 confirmed potentiometrically.

Clotting Time: A definite amount of milk was placed in a test tube, rennet added, the tube inverted twice, placed in a water bath at 38° C. and the time recorded. The tube was then tilted from time to time and when the milk failed to flow as a fluid the duration was taken as the clotting time.

(A) Effect of Concentration of Milk Components on the Rate of Coagulation.

The clotting time of milk varies with concentration of each of the substances involved in the process. None react at the same time, nor at the same rate. A latent stage precedes the clotting stage and each milk component involved reacts accordingly in this heterogeneous system. Expressed mathematically, the rate of clotting is a function of caseinate,

$$-\frac{dc}{dt} = f\,[\text{Caseinate}]\,[\text{Rennin}]\,[Ca{+}{+}]\,[H{+}]$$

rennin, calcium ion concentration and pH. The rôle of each of these variants in relation to milk clotting time was determined by maintaining all others constant.

(1) Variations in the *volume* of the medium may affect the velocity of reaction. The clotting constituents were prepared in gradually increasing amounts but with the same concentrations in each system. The

TABLE V

Relation between caseinate concentration and clotting time

Clotting System at 37° C. and pH 6.0 1% Rennin 0.2 c.c.		
5% Calcium Caseinate	0.2 N $CaCl_2$	Clotting Time
5 c.c.	1 c.c.	60 min.
10	2	32
20	4	17
30	6	10
40	8	8
50	10	6
60	12	5
70	14	5
80	16	4
90	19	4
100	20	2

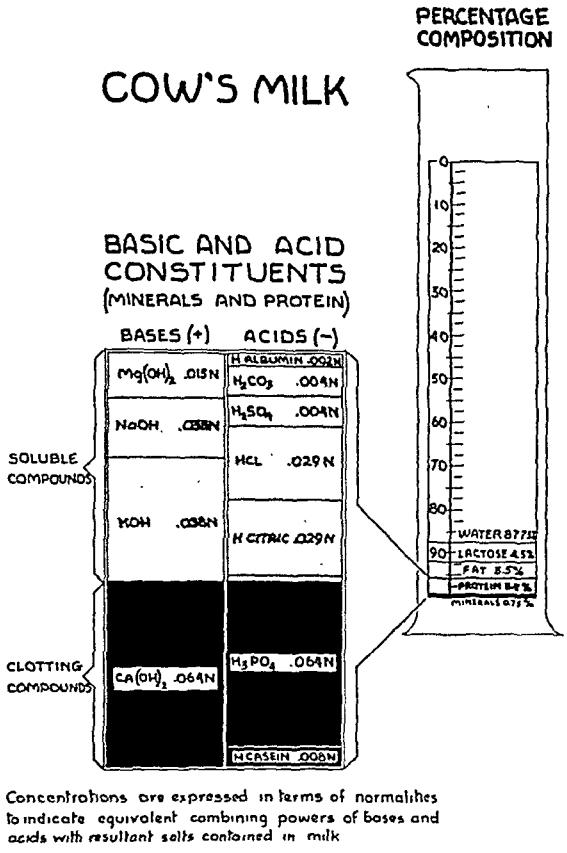


Fig. 1

clotting time was practically the same for each preparation. Apparently each of the clotting constituents react quantitatively upon one another according to chemical equilibrial relationships. (Table I).

(2) *Dilution* impedes velocity of clotting. The effect on milk was determined by adding increasing amounts of water to one series of clotting systems and finally adding large amounts of water to effect extreme dilution. While the clotting time diminishes rapidly, the rate is less than the degree of dilution. In fact beyond 1:100 the clotting time is practically constant. (Figure 2). The tough curd formed in the concentrated clotting system gives way to a gelatinous curd in the dilute system, then to a flocculent and finally to a gritty, in extreme dilutions. This effect on the character of the curd is due particularly to dilution of calcium ions.

Table III gives also the logarithmic values for each dilution and the clotting times respectively. The logarithmic curve (Figure 3) indicates an autocatalysis wherein rennin is reformed after reaction in the more concentrated clotting systems. And the tangent of the curve before becoming asymptotic is a measure of renning reformation. The horizontal curve indicates the prolonged but constant clotting time for spontaneous souring at every dilution. The curd tension varies inversely with the clotting time and the character of the curd is indicated. Similar relationships are graphed for the clotting of milk diluted with water in various proportions.

(3) Rennet concentration markedly affects the rate of milk clotting. Rennin splits caseinogen into paracasein, H+ increasing the velocity of Cleavage but Ca++ being unnecessary for this first stage in the clotting process. Table IV gives the data for the clotting systems graphed in Figure 4. With relatively large amounts of rennet, the clotting time is practically proportional to the rennet content. But with relatively small amounts of rennet the clotting times are prolonged rather indefinitely. There is an inverse proportionality between the amounts of rennet added and the resulting clotting time. In other words the clotting time is a logarithmic function of the rennet concentration. The character of the curd likewise varies with the rennet concentration—tough with rapid clotting times and flocculent with slow rates of clotting and small concentrations of rennet. The general equation maintains

(Rennet Concentration) . (Clotting Time) = Constant.

(4) Caseinate concentration is a determining factor in milk clotting. Experiments were set up maintaining all clotting constituents in each solution but varying the calcium caseinate content (Table V). The concentration-time curve (Fig. 5) parallels that of rennin. A definite chemical relationship exists therefore between caseinate and rennin for the course of clotting is quantitatively dependent upon their respective concentrations. The general equation maintains,

(Caseinate Concentration) . (Clotting Time) = Constant.

(5) Calcium Ion concentration modifies the course of milk clotting. Addition of calcium chloride decreases the pH of the synthetic mixtures as well as of

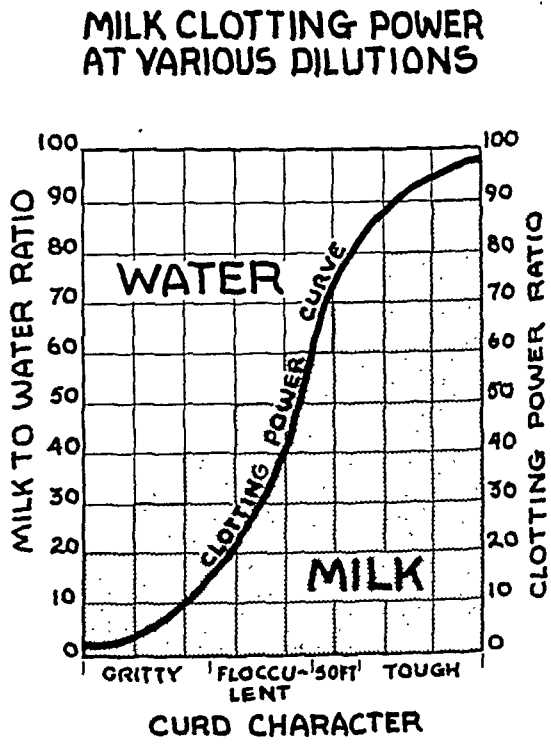


Fig. 2

TABLE VI

Relation between calcium ion concentration and clotting time

Clotting System at 37° C. and pH 6.5 5% Calcium Caseinate 25 c.c. 1% Rennin 0.2 c.c.	
Aq. $CaCl_2$	Clotting Time
0.01 N	91
0.03	72
0.05	50
0.07	32
0.09	20
0.11	15
0.13	12
0.15	7
0.20	4
0.40	1

milk. A millimol of $CaCl_2$ per liter reduces the pH by one unit. Calcium ions are necessary only for the second stage of clotting for rennin splits caseinogen into paracasein without the presence of calcium ions. If calcium is precipitated by adding sodium oxalate to

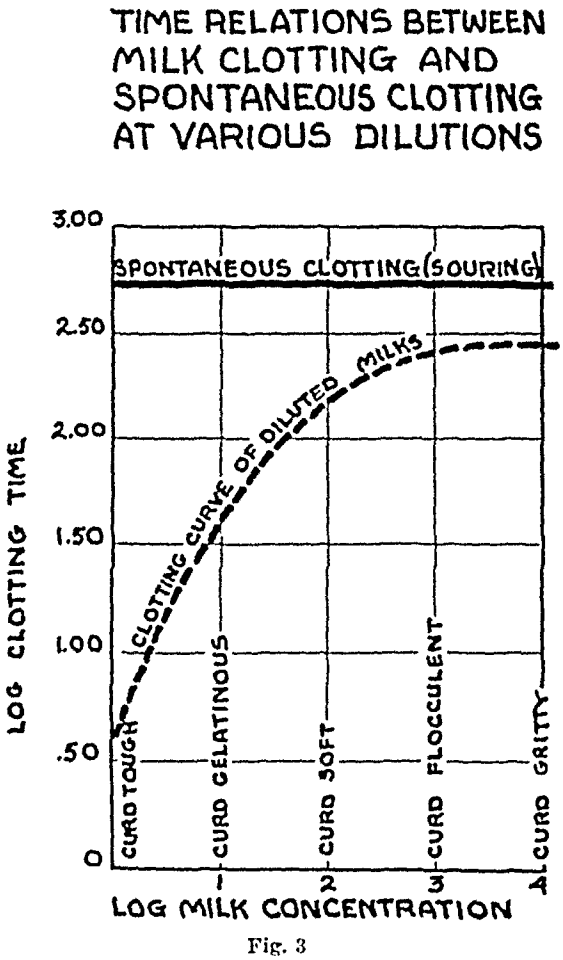


Fig. 3

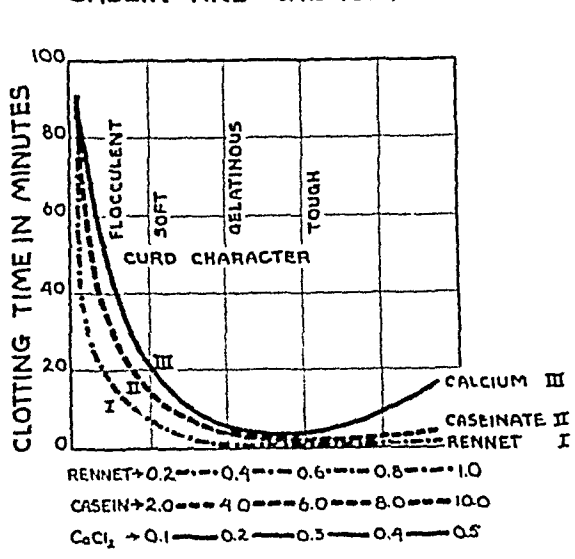


Fig. 4

milk or a synthetic milk mixture clotting does not occur on addition of rennin. If this solution is allowed to stand for an hour, then boiled to destroy rennin and $CaCl_2$ added clotting occurs. Rennin therefore acted upon carein without the presence of calcium. Any electropositive ion can replace calcium ions. Solutions with increasing amounts of molal calcium chloride were prepared for clotting time determinations (Table VI). Addition of Ca++ affects the state of aggregation and appearance of milk. It increases in whiteness prior to precipitation. The smaller the calcium ion concentration the greater the clotting time. This inverse proportionality maintains until 0.3 N calcium chloride when further increases in calcium ions actually prolong the clotting time (Fig. 5). Generally, however, the condition,

(Calcium Ion Concentration) . (Clotting Time) = Constant.

SUMMARY

1. Milk clotting involves the transformation of soluble caseinogen into some form of insoluble casein. With the action of rennin calcium paracaseinate is formed; with acid or heat, casein; and with more than one of these coagulants, a combination of these precipitates. Three constituents form the clot, caseinate, phosphate and calcium, consisting of but 2% of the composition of milk in the form of the largest molecular aggregates. The mechanism of milk clotting with rennin is similar to that of blood with thrombin, in the presence of calcium ions.

2. *The rennet clotting of milk is a diphasic autocatalytic process.* The first enzymic or digestive phase of clotting requires about half the time to develop the

curd, caseinogen being hydrolyzed into paracasein. Calcium ions are unnecessary for this stage in the clotting process. The second flocculation or active phase marks the appearance of calcium paracaseinate as a gel or precipitate. Calcium ions are necessary only for this second phase of clotting and both phases are accelerated by hydrogen ions. Calcium ions increase the whiteness of milk prior to flocculation.

3. The rate of clotting is a direct function of the concentration of the caseinate, rennin, calcium and hydrogen ions. The latter two prolonging clotting at higher concentrations. Diminution of any of these factors changes the character of the curd from tough to gelatinous, to flocculent and finally to gritty consistency at extreme dilutions, the curd tension varying inversely with the clotting time.

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Influence of Fat on the Absorption of Dextrose from the Human Alimentary Canal*

By

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DURING the past decade there has been a renewal of interest in the factors governing the absorption of dextrose from the alimentary canal. To a considerable extent this interest was initiated by Cori (1), who, in 1925, as a result of an ingenious method by which absorption of saccharides from the entire gastro-intestinal tract of rats was studied, came to the conclusion that (1) a proportionality exists between the absorbing surface of intestine and the body weight in growing male and female rats, and (2) the rate of absorption of hexoses is constant and is independent of the absolute amount and of the concentration of sugar present in the intestine. Trimble, Carey and Maddock (2) utilizing Cori's technic in dog's, made substantially the same observations. Magee (3) is also in agreement with Cori.

MacKay and Bergman (4), Pierce, Osgood, and Polansky (5), and Burget, Moore, and Lloyd (6), also employing Cori's method of study, made findings entirely at variance with those of the latter.

Ravdin and his associates (7), found that the rate of absorption of dextrose from a loop of intestine is increased with increase in concentration or volume of solution used.

Solutions of dextrose of varying concentration placed in the stomach are rapidly changed, so that when the solution reaches the small intestine the variations in concentration are of a small order. They suggest that this fact may explain the difference in the rate of absorption when the gastro-intestinal tract is used as a unit and when only a single segment of this unit is utilized.

As a rule absorption of a single foodstuff does not occur physiologically. It is important, therefore, to study the rate of absorption from mixtures of substance. Cori (8) has done this with combinations of 2 sugars, 2 amino acids, of sugars and amino acids, of dextrose and lactic acid, and of dextrose plus alcohol. It was found with great regularity, that when two substances were fed simultaneously, the rate of absorption of each was reduced. Thus, when dextrose and galactose are absorbed from a mixture of equal parts of these 2 sugars, the rate of absorption of both sugars is reduced to such an extent that the total amount of sugar absorbed is not greater than if dextrose alone or galactose alone were being absorbed. This is termed "mutual inhibition of absorption." This phenomenon was also present when a mixture of dextrose and glycine was given. Cori also states that absorption of dextrose from a pure solution proceeds much more rapidly than from a mixture of foodstuffs.

Experiments by Cajori and Karr (9) confirm the findings of Cori as to the rate of absorption of mixtures of dextrose and galactose from the intestines. Mahler and Nonnenbruch (10) found that (1) animal charcoal given with dextrose delayed absorption (2) mucin delayed absorption only when thoroughly mixed with dextrose (3) yeast stimulated the villi and increased the rate of absorption of dextrose.

The experiments described have all been performed on animals and are direct in character. It has been assumed that the results obtained are applicable to man.

AUTHOR'S STUDIES

From the foregoing review of the literature, it can be seen that but little work has been done on the question of absorption of dextrose from a mixture of foodstuffs. The results of an investigation by an indirect method of the influence of fat on the absorption of dextrose from the alimentary canal will be reported in this paper.

If a certain adequate amount of dextrose is given to an individual suffering from diabetes mellitus, a blood sugar

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curve of a certain height and length is obtained, which is of course higher than normal.

If the absorption of a certain amount of dextrose per unit of time produces a curve of a certain height, the absorption of a smaller amount per same unit of time in the same individual will give rise to a curve of lesser height, for the mechanisms which are concerned with the regulation of the concentration of dextrose in the blood will have less dextrose to metabolize. This also holds true for the glycosuria, which in any particular individual is directly dependent on the height of the concentration of dextrose in the blood: the greater the height, the greater the glycosuria; the less the height, the less the glycosuria. It has been shown by Wishnofsky and Kane (11) that if equivalent amounts of dextrose and starch are given to diabetics two days apart the curves for glycemia and glycosuria are identical. It is reasonable to assume that the same will hold true if equal quantities of dextrose are given two days apart. If on one of these days certain factors are introduced which will reduce the amount of dextrose absorbed, the curves for glycemia and glycosuria will be lower than on the day of control. It is this principle which is utilized in studying the influence of fat on the absorption of dextrose from the human gastro-intestinal tract.

METHOD OF PROCEDURE

Experiments were performed on eleven diabetics. To each of them 60 grams of dextrose, in a 20% aqueous solution, were given in the morning after a fast of 14 hours. Blood (venous) specimens were taken at the "fasting level" immediately before ingestion, 1½ hours and 3 hours after the ingestion of the dextrose. The sugar content of the blood was determined by the Folin-Wu method. The urine was collected at the end of 1½, 3, and 6 hours after the ingestion of dextrose, and its sugar content determined by Benedict's method.

Two days later, also in the morning after a fast of 14 hours, 60 grams of dextrose in a 20% aqueous solution were given and this was immediately followed by 120 grams of olive oil.* The blood was taken and the urine collected at the same periods as when dextrose alone was given. In the interval between tests the patients were on their customary diets. Those who had been taking insulin continued to do so.

ANALYSIS OF RESULTS

In Table I are recorded the concentrations of blood sugar and amounts of dextrose in the urine after the ingestion of dextrose and of dextrose and fat. Statistical analysis† reveals (1) that there is no significant difference in the concentrations of the blood sugar at the "fasting level," (2) that the concentrations of the blood sugar is significantly greater 1½ hours after the ingestion of dextrose, than after the ingestion of dextrose and fat. This also holds true for the glycosuria 0-90 minutes post cibum, (3) that there is no significant difference in the concentrations of dextrose in the blood three hours post cibum; nor in the glycosuria 1½ to three hours, and from four to six hours, inclusive, post cibum. How are these results to be interpreted?

TABLE I

Concentration of dextrose in the blood and quantity of dextrose in the urine of diabetics after the ingestion of 60 grams of dextrose and of 60 grams of dextrose plus 120 grams of olive oil

Case Number	Blood Sugar (mg. per 100 c.c. blood)						Urine Sugar (gm.)					
	Fasting Level		90 min. post cibum		3 hours post cibum		0-90 min. post cibum		90 min. to 3 hours post cibum		4-5-6 hours post cibum	
	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat
1	174	182	400	368	286	370	10.3	4.6	15.3	13.0	2.4	4.6
2	242	244	400	380	286	267	13.6	9.0	12.4	9.0	1.5	1.6
3	133	110	488	429	364	292	3.3	2.8	7.2	5.9	1.1	0.9
4	259	258	444	310	320	235	6.3	4.0	12.3	4.6	1.1	3.4
5	237	210	465	424	313	320	10.3	7.8	10.1	11.4	2.0	3.3
6	228	235	382	348	258	328	9.0	5.2	——	——	0.7	0.6
7	275	278	550	500	484	392	7.9	8.5	13.9	11.8	9.6	10.2
8	217	236	448	438	338	360	7.2	3.7	8.9	11.6	3.2	1.6
9	354	354	571	571	465	571	11.1	5.7	14.1	12.0	7.3	6.7
10	330	300	494	374	381	388	12.0	9.5	18.6	17.2	10.3	6.2
11	220	217	317	313	333	292	3.6	2.5	4.2	5.1	3.5	1.8
Means	243	239	451	405	348	347	8.6	5.75	11.7	10.15	3.88	3.72

It is at first necessary to take cognizance of the following: (1) It has been demonstrated quite conclusively that no appreciable amounts of dextrose are absorbed from the stomach. Absorption takes place almost entirely from the intestines. (2) It was observed by Ewald and Boas in 1886, and repeatedly confirmed, that fat decidedly inhibits gastric motility and secretion. It is not within the scope of this paper to enter into a discussion of the mechanism involved. The conclusions of Lim (12), who has done extensive work on this subject, may, however, be mentioned. He states: "Fat inhibits both the nervous and chemical phases of gastric secretion and motility. . . . Neither a nervous reflex, nor a reflex secretion from another organ is an essential mechanism of fat inhibition. . . .

*Olive Oil is 100% fat.

†The method of analysis used was that developed by R. A. Fisher (Statistical Methods for Research Workers, 3d, ed., London, Oliver and Boyd, p. 104, 1930).

This inhibition is probably brought about by a humoral mechanism." (3) We have found that fat, given alone in large quantities, to a large series of diabetics, does not in the slightest influence the concentration of dextrose in the blood. As this material forms the subject of another paper, it will not be elaborated on here.

It was stated above that the concentration of dextrose in the blood is significantly greater 1½ hours after the ingestion of dextrose, than after the ingestion of dextrose, and fat. (see Table I). This also holds true for the glycosuria 0-90 minutes post cibum. This effect may be produced by (1) slowing of the emptying of the stomach, or (2) reduction of the rate of absorption of dextrose from the intestines as a result of the presence of fat, or (3) both. That this effect is engendered entirely by the first factor, namely a retardation of the emptying of the stomach, is evidenced by the following: The concentrations of dextrose in the blood three hours after the ingestion of dextrose and of dextrose and fat are identical. The amounts of dextrose in the urine from 1½ hours to three hours, and from four to six hours, inclusive,—a period of 4½ hours, after the ingestion of dextrose and of dextrose and fat are not significantly different. (see Table I). This is an indication that the amount of dextrose absorbed when dextrose is admixed with large quantities of fat is the same as when dextrose alone is present in the intestine. During the aforementioned period, namely from 1½ to six hours, inclusive, after the ingestion of dextrose and fat, a sufficient amount of dextrose enters the intestine to admit of a rate of absorption equal to that of dextrose given alone.

DISCUSSION

In recapitulation, it may be stated that the study of absorption of mixtures of substances has not been extensive. Cori has performed a series of experiments using combinations of two sugars, of two amino acids, of sugars and amino acids, and of dextrose and alcohol. He has observed consistently that when two substances were fed simultaneously, the rate of absorption of each was reduced. This has been termed mutual inhibition of absorption. Thus, when dextrose and galactose were fed in a mixture, the total amount of sugar absorbed was not larger than if each sugar was fed separately. This was equally true when a mixture of dextrose and glycine was fed. Cori states categorically that absorption of dextrose from a pure solution proceeds much more rapidly than from a mixture of foodstuffs. Our results of a study of absorption of a mixture of dextrose and fat are in disagreement with this conception. We employed the gastro-intestinal tract as a physiological unit. Initially there is a reduction in the rate of absorption of dextrose which may be interpreted as a result of the retardation of the emptying of the stomach by fat. Soon, however, the rate of absorption of dextrose admixed with fat equals that of dextrose given alone.

SUMMARY AND CONCLUSIONS

1. A review of the literature on the absorption of dextrose from the gastro-intestinal canal is given.

2. The consensus of opinion is that dextrose is absorbed much more rapidly from a pure solution than from a mixture of foodstuffs.

3. An indirect method is described for the study of the absorption of dextrose from the alimentary canal of man.

4. Results obtained by this method indicate that the rate of absorption from the intestine of dextrose admixed with fat is not appreciably less than that of dextrose given alone.

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Enzymic Efficiency in Avitaminosis

VII. Peptic Digestion in Vitamin B Deficiency*

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THE literature on the efficiency of peptic digestion either in experimental polyneuritis or vitamin B deficiency in man is scanty and unconvincing. In 1926, Farnum (1) found feeding a beri-beri producing diet to a dog gradually decreases the total volume as well as the free and total acidity of gastric secretion. In the same year Cowgill and co-workers (2) reported that in mild cases of vitamin B deficiency in the dog, associated with anorexia, there is no marked change in the character of the hunger contractions. In the severe cases of this deficiency, in which anorexia is accompanied by nervous and muscular symptoms, there is gastric atony. Successful vitamin therapy is followed by a rapid improvement in tone of the stomach musculature. The only direct statement we are able to find in the literature concerning the influence of experimental polyneuritis or peptic activity is that of Farmer and Redenbaugh (3) who found marked reduction in peptic efficiency in polyneuritis columbarum in five pigeons. At that time (1925) the necessity for controlling the plane of nutrition was not fully appreciated. Recently Alvarez and co-workers (4) maintained two persons for six weeks and one for four weeks on a diet markedly deficient in vitamin B_1. The concentrations of hydrochloric acid and pepsin in the gastric juice were measured almost every day. In two subjects there were no definite changes in the gastric juice, and in the third the only changes consisted in two falls in acidity, each associated with a respiratory infection. These workers concluded: "The work here reported indicates that a diet deficient in vitamin B_1, by itself, is not likely to produce much reduction in gastric acidity. It is possible, however, that such a diet might reinforce the lowering effect on gastric acidity of fever induced by injections of foreign protein."

TABLE I

Influence of a deficiency of the vitamin B complex on peptic efficiency

Experiment No.	Animal Marking and Sex	Per cent of loss of Weight in Pathologic Animals	Peptic Digestion Expressed in Units Period of Digestion 30 Minutes	60 Minutes	90 Minutes
3394	P-M	22	1.75	0.96	0.67
	R-L.M		1.41	0.82	0.57
3491	P-DL.M	23	1.55	0.86	0.59
	R-DR.M		0.75	0.49	0.36
3302	P-M	23	1.47	0.86	0.62
	R-L.M		1.41	0.83	0.59
3416	P-R.F	23	1.62	0.85	0.58
	R-D.F		1.47	0.79	0.53
3398	P-R.F	24	1.65	0.91	0.59
	R-D.F		1.59	0.84	0.57
3399	P-DL.F		1.61	0.90	0.62
	R-DR.F	24	1.61	0.91	0.63
3423	P-R.M		1.79	0.94	0.66
	R-D.M	25	1.59	0.84	0.52
3392	P-DL.M		1.50	0.86	0.61
	R-DR.M	25	1.59	0.87	0.59
3395	P-R.M		1.78	0.97	0.67
	R-D.M	25	1.55	0.88	0.67
3353	P-DL.F		1.34	0.80	0.57
	R-DR.F	26	1.37	0.78	0.56
3355	P-R.M		0.94	0.60	0.43
	R-D.M	26	0.91	0.58	0.42
3305	P-F		1.34	0.79	0.56
	R-L.F	27	1.45	0.85	0.61
3397	P-F		1.39	0.84	0.57
	R-R.F	28	1.52	0.80	0.55
3304	P-DL.F		1.73	0.93	0.66
	R-DR.F	29	1.05	0.64	0.48
3303	P-R.F	50	1.58	0.86	0.66
	R-D.F		1.43	0.82	0.58

P = Pathologic; R = Restricted to the same plane of nutrition.

EXPERIMENTAL

Peptic digestion was studied in two series of experiments. A deficiency of the vitamin B complex was produced in 15 sets of animals and uncomplicated vitamin B_1 deficiency accompanied by varying degrees of polyneuritis in 24 sets of rats, according to the paired feeding technique previously described (5). The essential point of this feeding procedure is that the control animal of the same litter and sex was restricted to the same plane of nutrition daily as the avitaminotic rat. The composition of the rations is outlined in Table III. The control animals of the vitamin B complex set received Ration 1751 in which 10 per cent of the dextrin was replaced by an equivalent amount of Northwestern dehydrated yeast. The control animals of the vitamin B_1 set received the same ration as the polyneuritic rats but in addition 10 γ of Merck's crystalline vitamin B_1 daily.

The peptic digestion was studied according to the vicosimetric technique of Northrop (6). Twenty-five per cent glyceryl extracts were made of the stomachs in concentration of 1 to 20, ground with sand, shaken for 5 minutes, and allowed to stand at room temperature for 24 to 26 hours. The supernatant liquid was then decanted off and an equal volume of 25% glycerol added, shaken for 5 minutes, and recentrifuged. Kahlbaumm's casein was used, prepared according to Hammersten. The digestion was carried out in a thermostat at 37° C., employing the Oswald type of vicosimeters. The digestion was run at 10, 20, 30, 40, 50, 60, 70, 80, and 90 minute intervals. A

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total of 674 titrations were made in this investigation. To save space, we are reporting, however, only 30, 60, and 90 minute digestions. The results are expressed in pepsin units described by Northrop (6). All of the data are summarized in Tables I and II.

mate controls. In the rest of the experiments the difference in rate of digestion between the avitaminotic rats and their controls are too small to be of any significance. Summarizing all the results, the pathologic animals showed an increase in peptic diges-

TABLE II

Influence of vitamin B_1 deficiency on peptic effciency

Experiment No.	Animal Marking and Sex	Per cent of Loss of Body Weight	Degree of Paralysis	Peptic Digestion Expressed in Units Period of Digestion 30 Minutes	60 Minutes	90 Minutes	On Rations
3413	P-R.M R-D.M	14	Marked	1.53 1.24	0.84 0.73	0.59 0.53	1751 ; 2345 ; 3148-A ; 3148-X
3347	P-DL.M R-DR.M	18	Marked	1.67 1.68	0.94 0.93	0.65 0.64	3148-A
3478	P-R.M R-D.M	20	Marked*	1.28 1.27	0.76 0.75	0.54 0.51	1751 ; 2345 ; 3148-A
3401	P-M R-L.M	20	Moderate	1.59 2.30	0.96 1.27	0.68 0.81	3148-A
3480	P-R.M R-D.M	21	Marked	1.65 1.63	0.90 0.90	0.61 0.61	1751 ; 2345 ; 3148-A ; 3148-X
3372	P-DL.F R-DR.F	21	Marked	1.66 1.56	0.90 0.89	0.64 0.62	3148-A
3331	P-D.M R-R.M	22	Moderate	1.98 1.61	0.99 0.81	0.67 0.62	1751 ; 2345
3390	P-DL.F R.DR.F	25	——	1.78 1.50	0.95 0.85	0.64 0.58	1751 ; 2345
3379	P-DL.M R-DR.M	25	Marked	1.27 0.97	0.72 0.59	0.51 0.42	3148-A
3371	P-R.F R-D.F	26	Slight	1.31 1.04	0.83 0.64	0.58 0.47	3148-A
3360	P-DR.M R-D.M	26	Slight	1.22 1.32	0.74 0.78	0.59 0.90	1751 ; 2345
3376	P-D.F R-L.F	26	Marked	1.22 1.60	0.73 0.91	0.52 0.63	3148-A
3366	P-DL.F R-DR.F	26	Slight	1.35 1.02	0.80 0.62	0.58 0.49	3148-A
3410	P-DL.F R-DR.F	26	Slight	1.49 1.70	0.86 0.97	0.62 0.69	1751 ; 2345
3229	P-D.M R-DL.M	27	Slight	1.50 1.38	0.98 0.98	— —	1751 ; 2345
3342	P-R.F R-D.F	27	Slight	0.85 0.90	0.54 0.58	0.32 0.38	3148-A
3290	P-DL.F R-DR.F	26	Slight	0.91 0.92	0.58 0.67	0.43 0.43	1751 ; 2345
3291	P-DL.M R-DR.M	28	Slight	1.62 1.50	1.06 0.96	— —	3148-A
3374	P-DL.M R-DR.M	32	Slight	1.12 1.09	0.67 0.64	0.48 0.46	3148-A
3334	P-DL.M R-DR.M	32	Slight	1.53 0.86	0.84 0.57	0.58 0.35	3148-A
3329	P-D.M R-DL.	33	Slight	1.11 1.15	0.66 0.72	— —	1751 ; 2345
3362	P-DL.M R-DR.M	38	Marked	1.42 1.23	0.89 0.93	0.59 0.52	3148-A
3344	P-M R-L.M	40	Slight	1.25 1.51	0.76 0.88	0.56 0.62	3148-A
3268	P-DLR.M R-LDR.M	41	Marked†	1.40 1.54	0.82 0.89	0.59 0.62	3148-A

P = Pathological; R = Restricted to the same plane of Nutrition.
* Slight Convulsions.
† Marked Convulsions; cart wheels.

Peptic Digestion in a Deficiency of the Vitamin B Complex. In only two groups, 3491 and 3304, marked differences in rates of digestion have been observed. In each of these cases the pathologic animals have shown a more rapid rate of digestion than the litter

tion in the 30, 60 and 90 minutes to the extent of 14.3, 11.9, and 10.9 per cent respectively. There was no influence on the rate of the loss of body weight on rate of peptic digestion.

Peptic Digestion in Vitamin B_1 Deficiency Asso-

TABLE III
Composition of rations

	Number of Rations			
	1751	2345	3148-A	3148-X
Casein (Commercial)	—	—	16	16
Casein[1]	20	10	—	—
Salts No. 185	4	4	4	4
Agar-agar	2	—	—	—
Butterfat (filtered)	10	10	—	—
Dextrin	64	61	—	—
Autoclaved beef[2]	—	15	—	6
Autoclaved Fleishman's Yeast[3]	—	—	12	9
Cod liver oil	—	—	2	2
Cornstarch	—	—	57	54
Unfiltered butterfat	—	—	9	9
	100	100	100	100

1. Washed for 10 days with acidulated water and extracted thoroughly with 25 per cent alcohol.
2. Autoclaved for 6 hours at 20 pounds pressure at the natural pH of the beef (round steak).
3. Dehydrated Fleishman's yeast autoclaved for 5 hours at 15 pounds pressure at the natural pH of the yeast.

ciated with Polyneuritis. There was considerable variation in rate of digestion of the 23 groups studied. Fourteen pathologic animals showed varying degrees of increase in the rate of peptic digestion compared with their litter mate controls restricted to the same plane of nutrition, while nine avitaminotic rats showed varying degrees of decrease in peptic activity compared with their controls.

Summarizing all the results for the 30, 60, and 90 minute periods of digestion, the pathologic rats showed an increase over their controls of 6.9, 3.5, and 3.7 per cent respectively. Varying degrees of paralysis and increase in per cent of the loss of weight had no noteworthy influence on the rate of peptic digestion.

CONCLUSION AND SUMMARY

The data presented in this paper conclusively demonstrates that neither in a deficiency of the vitamin B complex nor in vitamin B_1 deficiency associated with varying degrees of paralysis is there any significant change in the rate of peptic digestion when comparisons are made with litter mate controls of the same sex and restricted to the same plane of nutrition.

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Unusual Course of Pelvic Abscess and Fistulous Tract*

By

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THIS case is reported because of the long continued ailment and the very great distance between the source of infection and the external pointing of the abscess.

CASE HISTORY

The patient, male, nineteen years, was referred to me by Dr. Charles Clayton, orthopedic surgeon, with the following history:

In March, 1932, he developed an abscess on the outer middle third of the left leg, accompanied with the usual symptoms: pain, redness, swelling and elevation of temperature. He went to the City-County Hospital where the abscess was opened and drained. He was discharged in two weeks. *Two months later,* the patient had a recurrence accompanied by a discharge near the old scar. He returned to the hospital. A diagnosis of osteomyelitis of the descending ramus of the left ischium was made. He was operated on and a cast applied. He remained this time in the hospital for ten weeks, being discharged the last week of *August, 1932.*

Three weeks after leaving the hospital, the patient noticed that he had some drainage from the original opening. That condition continued until July, 1933. He was again hospitalized and drainage instituted, by wide exposure of the femur on its lateral aspect. He was discharged at the end of ten weeks. When he left,



Fig. 1. Roentgen film after injection of fistulous tract with opaque substance. The size, course and internal termination of the tract are well demonstrated.

*Read at the Annual Meeting of the American Proctologic Society, Kansas City, Mo., May 11, 1936.
Submitted May 19, 1936.

the wound had apparently healed; however, in about three weeks he noticed some drainage, and had more or less drainage until June, 1935, when he was again sent to the hospital and operated on. After another ten weeks in the hospital he was discharged September 5, still with some drainage.

The latter part of October, 1935, the patient was



Fig. 2. Foreign body removed from pelvic termination of fistulous tract (slightly enlarged).

sent for X-ray study to Dr. X. R. Hyde, who was able to demonstrate that the sinus extended inward to the rectum. Shortly afterwards, I saw him in consultation with Doctors Clayton and Hyde. At that time, after careful study of X-ray plates along with proctoscopic examinations, I became convinced that the source of infection was in the anal canal.

The patient was sent to the hospital and on January 20, 1936, under avertin anesthesia, an antero-posterior incision was made in the left ischiorectal fossa, exposing the levator ani. The main tract was easily recognized by the great amount of granulation tissue lining it. A careful search was then made along the floor and sides of the exposed tract for off-shoots. I was now able to follow the main tract up between the sphincters and just as I got to the internal opening, I found what we believed to be the source of infection, namely, a foreign body about ⅞ inch long and ⅛ inch wide with ragged edges.

The main tract, including the external sphincter, was incised. All overlapping edges of skin and mucous membrane of the tract and fossa were removed. The wound was lightly packed with vaseline gauze.

POST-OPERATIVE TREATMENT

The sinus down the thigh was irrigated daily with hydrogen peroxide for about one week. The wound was irrigated every four hours with warm normal saline solution.

Drainage from the external sinus ceased about the sixth day. The ischio-rectal wound filled in rapidly. Temperature returned to normal and remained so, after four years of considerable elevation at times. The patient gained weight rapidly and has been working since March 1.

The interesting thing about this case would appear to be, did this patient have the anal infection before the osteomyelitis? I am inclined to think that he had, and that such infection was the reason for failure of previous operations although they were performed by skilled men.

Pepsin Versus Hydrochloric Acid in the Experimental Production of Gastric Ulcer*

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and

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THE etiological factors in the production of gastric and duodenal ulcer in man have not been established (1, 2, 3). Peptic ulcers simulating those occuring in man, were first experimentally produced in dogs by Exalto (4) and Mann and Williamson (5). These investigations have been thoroughly reviewed by Graves (6). The effects of acid gastric chyme have been particularly stressed by most authors.

Buchner, Siebert and Malloy (7) have reported that subcutaneous injections of histamine produced ulcers in the prostomach of the rat. These authors as well as Burkle de la Camp (8) contended that the resultant increase in hydrochloric acid and possibly pepsin was responsible for these ulcers.

Both clinically and in animal experimentation the acid portion of the gastric chyme has been regarded as of greater importance than its pepsin content (9). Recent clinical observations of Vanzant, Osterberg, Alvarez and Rivers (10) and confirmed by Mullins and Flood (11), seem to indicate that peptic ulcer in man is frequently accompanied by an increase of pepsin.

It occurred to us therefore that a more direct approach to this problem could be made by controlled feeding experiments on rats, employing solutions of pepsin with hydrochloric acid and hydrochloric acid alone (12).

EXPERIMENTAL

Rats of the original Wistar strain, averaging in age 4 months were fed the Steenbock-Bills diet (13). Fresh lettuce or sliced carrots were added on feeding days. Fluids were supplied by means of stoppered flasks, with glass tube outlets attached to the cages. The rats were then able to partake of these solutions *ad lib.* At first we used a 20% solution of pepsin in 0.3% HCl. We have subsequently found that a concentration of pepsin as low as 1% is equally as effective.

These rats were divided into *two main groups:* a fasting

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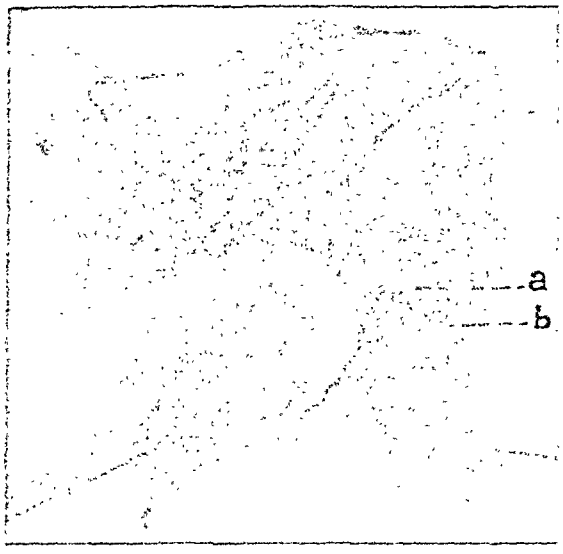


Fig. 1. Photograph of a portion of the pro-stomach of a rat showing a typical ulcer-like, gross lesion of the mucosa. Note the raised margins (a) and central depressed area (b) of the lesion.

and a non-fasting. In the *fasting group*, the rats were fasted for two days and were fed on the third, in recurrent cycles. The *non-fasting group* had continuous access to food. The experimental periods varied from 12 to 21 days, averaging in general about 16 days. The results in the fasting group are summarized in Table I.

RESULTS

In the fasting *Sub-group 1a*, which had continuous access to a 20% (by weight) solution of granular pepsin (1:10,000 Parke, Davis and Co.) in 0.3% hydrochloric acid we found that 96% developed one or more ulcer-like gastric lesions.

On the other hand, in a control *Sub-group 1b* that received only 0.3% HCl under similar conditions, only 16% developed these gastric lesions. In order to establish that the greater incidence in the pepsin hydrochloric acid *Group 1a* was actually due to the activity of the pepsin and not to any foreign substance it might contain, a group of animals received a mixture

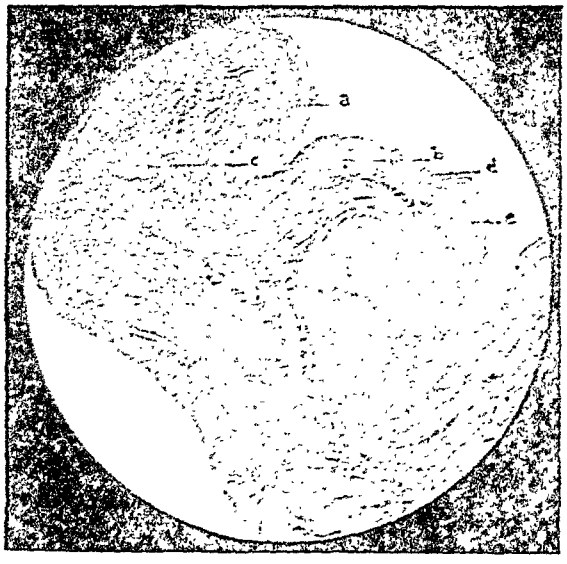


Fig. 2. Photomicrograph of a section of pro-stomach of submucosa (a) detaching the muscularis mucosae (b) from a *normal rat*. Note the intact submucosa (b) and its close proximity to the overlying mucosa (a) as well as to its underlying muscularis (c). The layers of stratified squamous epithelium are normal in every respect. The superficial cells (d) present only slight desquamation and the basal cell layer (e) is entirely intact.

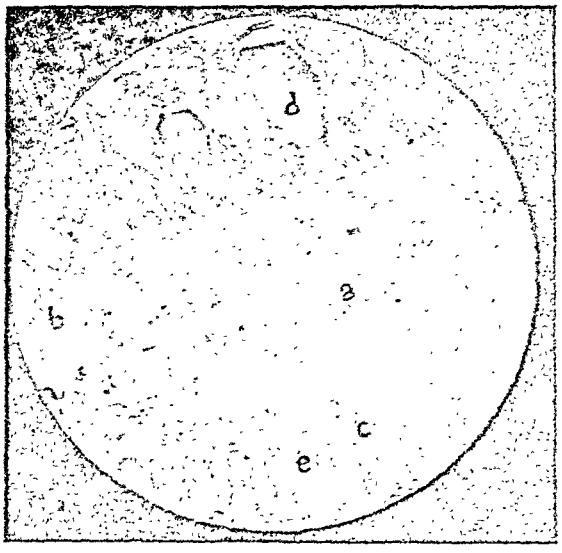


Fig. 3. Photomicrograph of a section of *a typical lesion* described in the gross. Note the marked edema of the submucosa (a) detaching the muscularis mucosa (b) from the underlying muscularis (c). Note also the extent of the infiltrate into the papillary bodies (d) and separation of the bundles of the circular layer of muscle (e).

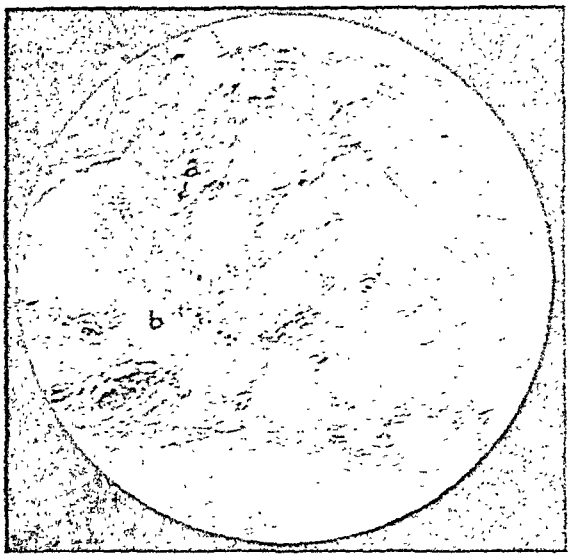


Fig. 4. Photomicrograph of another typical lesion showing marked desquamation of the lining epithelium. Note the point of complete denudation of the lining (a, with arrow) and the congestion and infiltration accompanying the edema in the submucosa (b).



Fig. 5. Photomicrograph of another typical lesion showing the disturbance of the basal layer of epithelium by the advancing infiltrate from the submucosa through the muscularis mucosae (a, with arrow). Note also the moderate degree of desquamation of lining epithelium (b) as well as congestion, edema and infiltration in the submucosa (c).

of inactivated pepsin (heat digestion) and hydrochloric acid. In the latter group we observed lesions in only 20% of the rats. This incidence almost corresponded to that of *Group 1b* that had received hydrochloric acid alone. This appears to establish that the far greater incidence in the pepsin hydrochloric acid group was definitely due to the activity of the pepsin.

That fasting was not the sole cause of these lesions appears to be established by the fact that in *Group 1d* 15 rats with similar fasting periods and continuous access to water alone, no gastric lesions were observed.

The results in the *non-fasting Group 2*, which had continuous access to food are summarized in Table II.

In the *Sub-group 2a*, which had continuous access to a solution of pepsin and hydrochloric acid, we found only 20% developed gastric lesions as compared to 96% incidence in a similar *group 1a* subjected to fasting periods.

Furthermore, no lesions were observed in the *Sub-group 2b* that had continuous access to HCl alone, as compared with an incidence of approximately 16% in rats under similar conditions in the fasting *Group 1b*. Although the absolute incidence of gastric lesions in the non-fasting 2a and 2b is not as great as in the fasting group, the relative incidence is similarly apparent.

To further establish that no foreign substance was present in the pepsin preparation, 20% dry pepsin (by weight) was incorporated in the diet. No gross lesions were observed in any of these rats, 2c. In 60 additional control rats, 2d, on various complete stock diets, no gross lesions were observed at autopsy.

DESCRIPTIONS OF LESIONS

Before describing the observed lesions, the normal anatomical findings in the rats' stomach may be briefly reviewed. The rumen or prostomach is sharply divided from the glanular portion by a smooth, elevated linear ridge, which passes to either side of the cardiac orifice. Histologically, (Fig. 2), the rumen, including the limiting ridge, is lined with squamous epithelium, covered by a thin keratin layer. The epithelium rests almost directly upon the well developed muscularis mucosae, from which it is separated by delicate connective tissue. The muscularis mucosae is separated from the muscularis by areolar connective tissue of the submucosa.

Gross Description: The observed lesions (Fig. 1) were frequently situated in proximity to the limiting ridge and along the lesser curvature. However, other portions of the rumen were often similarly involved. These lesions, which varied in number, were usually discrete, though at times they appeared confluent. Their margins were raised and the base of the umbilicated center appeared brown or red. They measured approximately 0.5 to 5 mm. in greater diameter.

TABLE I

Group 1. Fasting group

Sub-Groups	No. of Rats	B. S. D. = Bills Stock Diet	Mean initial body weight gm.	Mean final body weight gm.	Duration of experiment days	Autopsy findings	No. of lesions	No. of rats without lesions	Percentage of rats with lesions %
a	30	B. S. D. + .3%, HCl + 20% Pepsin. Fasting periods 48 hrs.	190	183	12 to 21	Multiple lesions in 29 rats.	1 to 8	1	96
b	18	B. S. D. + .3% HCl. Fasting 48 hrs.	275	202	21	2 rats—3 lesions, 1 rat—1 lesion.		15	16
c	10	B. S. D. + .3% HCl + 20% inactivated Pepsin. Fasting 48 hrs.			12 to 21	Multiple lesions in 2 rats.		8	20
d	15	B. S. D. + water. Fasting periods of 48 hrs.			28			15	0

TABLE II

Group 2. Non-fasting group

Sub-Groups	No. of Rats	B. S. D. = Bills Stock Diet	Mean initial body weight gm.	Mean final body weight gm.	Duration of experiment days	Autopsy findings	No. of lesions	No. of rats without lesions	Percentage of rats with lesions %
a	10	B. S. D. + .3% HCl. 20% Pepsin. No fasting.	165	152	13 to 21	1 rat—6 lesions. 1 rat—1 lesion.		8	20
b	10	B. S. D. + .3% HCl. No fasting.	261	237	21	Negative.	0	10	0
c	8	B. S. D. + 20% Pepsin (dry). No fasting.			28	Negative.		8	0
d	60	Additional controls on various stock diets.			21	Negative.	0	0	0

Microscopic Description: The most constant finding consists of focal areas of submucosal edema, which detach the muscularis mucosae from its underlying coat and which in areas also involve adjacent mucosal as well as muscular layers. In the latter coat, the edema produces separation of the bundles of the inner circular layer of the muscle while in the former (mucosal layer) the edema of the papillary bodies produces wide separation of the epidermal pegs. In most of the areas a pronounced cellular infiltrate and increased vascularity accompany the edema. The exudate consists of extravasated red cells and varying numbers of polynuclear, round and plasma cells (*Fig. 3*).

The extension of the above described infiltrate of the submucosa into the basal layer of the epidermis, distorting the normal architecture of the latter, especially, in the latter region of the stratum germinativum, is of especial interest.

Other less extensively involved areas, present in addition to the edema, congestion and increased number of blood cells. The above changes are most marked at sites corresponding to the elevated margin of the lesions described in the gross.

A less constant finding consists of desquamation of the lining epithelium in the center of some of these lesions. In areas, the process is advanced to a degree deserving the term "erosion," since the mucosa at these sites is almost completely denuded. At times the desquamation is observed to the degree of complete denudation of the lining membrane.

DISCUSSION

These experiments would seem to prove that pepsin rather than hydrochloric acid is the important agent in the experimental production of gastric ulcer in the rat. While our work was in progress, Howes, Flood and Mullins (14) reported that operatively produced gastric defects in cats showed a greater delay in healing in those receiving pepsin with acid, as compared to those receiving acid alone.

The selective localization of these lesions in the rats' prostomach is of extreme interest. This region is lined by squamous epithelium (a site unusual for peptic ulcer in man). Ulcers only occur occasionally in the glandular portion both in our experiments and in those reported with histamine injections (7, 8). Why histamine (15, 16) and a pepsin containing acid extract of pigs' stomach (17) produced gastric lesions in cats and dogs (lined by glandular epithelium) and why with similar agents in the experimental rat, the prostomach (lined by squamous epithelium) was the seat of election for these lesions, remains unanswered at present.

The dependence of these lesions upon alternating fasting periods, as evidenced by a 96% incidence in the pepsin-HCl fasting group, compared to only 20% in the non-fasting group is likewise very significant. In the light of possible amino acid deficiency, originally suggested by Weiss and Aron (18) experiments are in progress with the simultaneous administration of histidine monohydrochloride and other essential amino acids. The results will be published.

This rapid and simple method of ulcer production in a readily obtainable laboratory animal should afford opportunity for the further study of the role of pepsin in the activation and tendency toward chronicity of peptic ulcer in man.

CONCLUSIONS

1. Pepsin in an acid medium is far more effective than is hydrochloric acid alone in the experimental production of ulcer-like gastric lesions in the albino rat.
2. Fasting appears to be a very important factor.
3. This rapid method of producing ulcers is suggested for the study of the prevention and the treatment of peptic ulcer.

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Editorials

IN WHAT WAY DOES A FULL STOMACH ADD TO THE TROUBLES OF A FAILING HEART?

IT must always be disturbing to a gastro-enterologist to hear that the elderly man whom he treated for a time for flatulent indigestion dropped dead a few months later with an attack of angina pectoris. The questions will then arise: Was not the man's feeling of gas pressure the earliest symptom produced by the diseased coronary artery, and should not this possibility have been suspected in time so that the man could have been protected from the dangers of overexertion? What was there peculiar in this particular history which should have warned the physician that he was dealing with a *failing heart and not with an* upset stomach or a diseased gall bladder?

In looking back over the histories of some of these patients one finds little that could have warned a physician as to the true state of affairs. Often there is no question about the fact that the distress was in the epigastrium and not in the chest; sometimes it was almost in the gall bladder region, and in some cases there were good reasons for diagnosing cholecystitis. In other cases heart trouble was thought of, because in some ways the story suggested it, but unfortunately there were so many elements that pointed to a neurosis that when the electrocardiogram was reported as almost normal, the thought of coronary disease was dismissed. Perhaps in most of the cases the story indicating heart disease either was not elicited or else was not given sufficient attention.

Now what are the symptoms that should have been looked for in a man past middle age complaining of pressure distress or pain in the epigastrium? The most diagnostic one would have been that this distress followed, not the taking of food, but exertion, and particularly exertion after eating. On being questioned more carefully, the man might have stated that after eating he could not walk a block without getting the distress so bad that he would have to stop and wait a few minutes until it passed off. Perhaps also, if the man came from the colder parts of this continent he might have remembered that the pain came sooner if he tried to walk *in freezing* weather.

Or if the man was accustomed to dig in his garden or to play golf strenuously over the week-end he might have noticed that he usually had a restless gassy or wheezy night after this extra exertion. Commonly such a patient will be found to have a high blood pressure. Many of these people with hypertension seek out the gastro-enterologist because they belch or feel distended with gas.

For many years, and probably since the time of Hippocrates, we physicians have been accustomed to recognize the type of patient who cannot exercise after a good-sized meal, but we have probably been wrong in assuming that this difficulty arises because the full stomach presses up on the heart. Although it is possible that the heart's action can be disturbed in so simple a mechanical way, it now seems more probable that the embarrassment of the organ arises in the fact, well demonstrated by Herrick et al (1) and McCracken et al (2) that after a meal, the blood flow more than doubles, not only in the blood vessels supplying the digestive tract, but also in all the vessels of the rest of the body. Now that this has been demonstrated, one can easily see why a man whose heart is ordinarily just strong enough to stand the extra strain of a short walk is not able to take this walk after meals when the load on the circulation has already been increased almost to the breaking point.

Walter C. Alvarez, Rochester, Minn.

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COLONIC "VOMITING" DUE TO FAULTY EATING

"WHO hath put wisdom in the inward parts, or who hath given understanding to the heart?" (1). By means of this power for "reasoning," the heart automatically controls the circulation of the blood. But may there not be still unknown "wisdom" in other inward parts? Does not the stomach exhibit "wisdom" when, as the result of overindulgence, it rejects what has been put into it by the abnormal act

Submitted February 20, 1937.

of vomiting? It does; for, through such act, this "primary" digestive pouch serves to protect the body from the absorption of injurious substances in extremely unsuitable food. Moreover, in another act of the digestive system as a perfect nutritive apparatus, according to the hypothesis of Burnett, the large gut appears to serve as a "secondary" digestive pouch. The proximal colon, by analogy, should exhibit a power of "reasoning" similar to that of the stomach; for in it, when food consumed has been thoroughly comminuted, made complete and properly proportioned and is not mixed with laxatives, the aliment is retained. It is kneaded back and forth by waves of peristalsis and antiperistalsis, and thus completes its cycle of digestion and absorption (2). But when the ingested mixture is abnormal, the colon "vomits," as is manifested by diarrhea or soft stools. Thus, this "secondary digestive pouch" serves to protect the body from the absorption of injurious substances contained in unsuitable food.

The proof of this action is not only shown by abnormal forms of the feces but also by an abnormally fast passage of a marked evening meal through the bowels, *i.e.* a rapid intestinal rate (3). In these circumstances, while the dejections may be irregular, yet a portion of this meal, delimited with seeds or another marker, is frequently discharged in about thirteen hours, and at the latest, is seen in about sixty-three hours. Whereas, when the colon is not "vomiting," one, and sometimes two, entirely segmented or normal stools are common daily: yet such meal residues do not appear for about sixty-two hours, and, at the latest, are seen in about one hundred and thirty-four hours. *Such time is considered to be the normal intestinal rate.* The method of testing it appears to be the most exact way of knowing about the nutrient substances which are assimilated by cells in the final and most important phase of "anabolic" or normal nutrition.

The construction and maintenance of the cells from this point of view receive support from established physiological principles. In the *first* place, if completely segmented feces are normal for the higher animals, it is reasonable to suppose that they are normal for the highest animal, man. *Second,* the formation and action of the proximal colon which molds these segments is normal for the higher animals; for there the aliment is kneaded back and forth, and then a segment from its contents is, every now and then, nipped off by a ring of constriction, and carried away to be moulded, (in its further passage down the colon) to the firm fecal nodule (4). A rapid passage of the colonic contents in animals, due to unsuitable food, has been observed (5). This is abnormal and can be regarded as "vomiting" by the colon. The slow passage of uniform segments of the intestinal contents through the distal colon of man has been described by Fischl and Porges (6); and this is the normal. Whereas, the rapid and propulsive passage of large and irregular masses of the colonic contents from caecum to rectum of man has been observed by Holzknecht (7); this is abnormal: it is a sign of "vomiting" by that part of the bowel. According to this hypothesis, when the molding of formed stools in the secondary digestive pouch prevents such "vomiting" by the colon in patients whose diets are adjusted and erroneous ways of eating are avoided, it is reasonable to presume that such action of the proximal colon is normal for man. *Third,* when patients, and especially those in a "health class" for skin diseases at the Massachusetts General, and in one for arthritis at the Peter Bent Brigham, Hospitals, apply these measures, frequently they become relieved of the consequences of a faulty diet, and become healthy. Furthermore, since some diseases have for a long time been supposed to be of *metabolic* origin but such were without sound and scientific principles by which they could be treated, now through the understanding and application of the *anabolic* processes, the previously unrecognized cause of some of the "metabolic" diseases may be removed (8, 9).

From this point of view, "health" becomes not always a vague and variable condition of the human body, as ordinarily thought but, at times, may be an exact and improved state of well-being about which relatively little is yet known. To create optimum health, patients are advised to eat very slowly, to avoid the consumption of irregular, incomplete, and disproportioned meals and to abandon the use of laxatives. By such cautions, the patient is supposed to benefit from the food consumed. Only giving patients lists of food is valueless in support of these principles. Each patient must learn to operate his own nutritive apparatus normally by *how* and *what* he eats. In place of such hap-hazard directions, our patients are requested to keep a week's record of their nutrition, by writing down all the food consumed, the time spent at meals, the time and kind of their dejections, and to perform a test of the "intestinal rate." These records are kept and examined every few weeks in the beginning of treatment. When "vomiting" by the colon is evident, further "health" adjustments are advised in accordance with the requirements of *each* subject. After the records show stools of normal character and the time required for a meal to pass through the bowel is within normal averages, often one observes that the red, scaling, and disfigured skins of patients with eczema or psoriasis, or the swollen, stiff, and painful joints of arthritis which have existed for long periods, become relieved. In these circumstances, since a state of "health" has been created which relieves disease, it seems obvious that this state of nutritional health subsequently must be controlled in order to prevent recurrences. If these principles of dietary and physiologic treatment are continutd, such results can be accomplished (10). Former patients are required constantly to observe their dejections and to keep them normal and to obtain two sets of normal figures of their intestinal rates and of their weights each month. When these results are abnormal the patients are advised to return for discussion of their disturbances or are enrolled in the "health class" immediately. Even when they are well, these healthy persons are advised to return several times a year with required figures and a week's record of their food-intake so that the physician is convinced that they continue to be normally nourished and healthy. At one of these visits, a thorough and exact "health" examination is made; this gives subjects added assurance that, when they prevent their colons from "vomiting" by taking proper food and by careful living, they are able to control the exact and the improved state of health which has followed from *"anabolic nutrition"* and which has acted favorably upon their ailments.

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Book Reviews

Les atrophies gastriques dans les anémies idiopathiques et les mé tanémies. By Robert Lehmann. Le Francois, Paris, 1936, pp. 118, 5 plates.

A COMPARISON of the different forms of anemia with the condition of the gastric mucosa is attempted. It is entirely based on gastroscopic observations. X-ray findings have been considered also, but the author does not attribute much of value to them. The cases of idiopathic anemia observed clinically and gastroscopically have been subdivided into four groups: (1) Anemia of Biermer, (2) Hypochromic achylic anemia (or severe chlorosis), (3) Aplastic anemia, (4) Intermediate malignant anemia (Chevallier), containing those malignant cases which do not correspond with any of the other groups. The atrophy of the gastric mucosa is subdivided as usually into patchy and diffuse atrophy. 19 observations are reported extensively, but this figure appears to be not entirely sufficient to justify all the conclusions. However, it is of great importance that the author confirms an observation made at first by Jones, Benedict and Hampton, namely that the atrophic areas respond to therapy and that regeneration of the atrophic mucosa is possible. He believes that usually the patchy atrophy is healed by liver treatment, and that diffuse atrophy responds to iron. The bibliography is excellent, and the small book will be of great value to the hematologists as well as the gastro-enterologists.

Rudolf Schindler, Chicago, Ill.

Physiology in Health and Disease. By Carl J. Wiggers, Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Second edition. Cloth, 1124 pages with 191 engravings. Price $9.00. Lea and Febiger, Philadelphia, 1937.

THE appearance of a second edition two years after the first printing indicates the favorable reception which this publication has received and is further evidence of the author's efforts to keep abreast of current developments in physiology and clinical medicine. As with the first edition, this edition is intended primarily as a textbook for medical students but it is written in accord with the author's conviction that clinical medicine should be approached from the physiological aspect since disease is essentially Nature's experiment in physiology. The book stresses the application of pure science to physiology, inculcates general principles of physiology, outlines and surveys the function of various tissues, organs and systems and emphasizes in masterly fashion the methods and procedures by which physiological knowledge is adduced. Having devoted a lifetime to an unusually fruitful investigation of the heart and circulation, the author has treated these subjects most exhaustively and with a degree of success probably not approached by any other publication. The other organs and systems of the body in both health and disease are also thoroughly considered. In partial evidence of this fact it may be noted that approximately 100 pages are devoted each to the gastro-intestinal tract, respiration, blood and blood formation, metabolism and nutrition, endocrine organs and reproduction and nearly 200 pages to the nervous system. In the second edition a number of physiological concepts have been recast or amended to make a readjustment of emphasis in accordance with the rapid progress of contemporaneous research, clinical material has been used to even a greater extent in discussion of physiological principles and clinical conditions have been analyzed as completely as possible by application of facts and concepts established by experimental means. Unusually abundant references to the American, English, French and German literature are given. Especially valuable is the listing of nearly all the outstanding review articles, monographs and texts recently published in this field. To the student of physiology or the clinician who seeks the ultimate exposition of body processes in health and disease, this book will be invaluable.

J. P. Quigley, Cleveland, Ohio.

Man the Unknown. By Alexis Carrel; Harper & Brothers, $3.50, 322 pages and index.

IN this book Carrel states that if an intelligent man continued to study exclusively until he was fifty years of age, he could probably acquire by that time a good working conception of all existing human knowledge. Carrel himself, having had ample opportunity, has probably come nearer to fulfilling this particular condition than any other man alive. With the advantage of this training he sets out in this book to summarize all of the extant knowledge about man. The book is the first scientific attempt of this kind in history, and though it may have the faults of first attempts, nevertheless it has many excellent points.

Carrel points out that of all the things that man knows, that which he needs the most and knows the least, is a thorough knowledge of man himself. He indicates that civilization carries with it the seeds of its own destruction. The records of the past confirm this; each civilization has slowly risen to a climax and

then rapidly crashed. Our civilization is the first one in known history which is conscious of its own impending destruction and has sufficient knowledge on hand to know how to prevent it, if it will only get busy. Will we do that? asks Carrel.

The only way to begin it, is to go at it in some such way as he is doing, by first collecting and correlating all knowledge concerning man himself.

In his summary of the knowledge of man he goes down to fundamentals and begins with physics and the philosophy of physics. He stimulated the reviewer to secure Bridgman's book and master the theory of the operational concept, and has found it valuable in daily medical practice all the way from working out a complex diagnosis to evaluating a drug advertisement. Chemistry, anatomy, physiology, are all rapidly and carefully summarized. From the amount of space devoted to psychology, or the mental aspect of man, one concludes that Carrel considers this phase of man the most important in the problems to which the book is devoted.

He incidentally touches on the fields that are not at present recognized as scientific. He discusses quite frankly the reported phenomena of mysticism, telepathy, clairvoyance, and miracle cures. This feature of his book has produced no small sensation among its readers, especially those in the medical circles. The publishers rode it as hard as they could as a publicity stunt. However, on careful examination it will be found that this feature occupies about the amount of space and has received about the amount of attention that it deserves. Carrel gives no impression of having been carried away by these things; he has observed them and is interested and is watching them in a scientific way.

Human ecology has received some original treatment. He demonstrates man as the most adaptive of all living organisms to external environment, but as unable to adapt to the environment which he himself builds up about himself. Man builds up civilization to which he cannot adapt. He is not adapting to the present civilization. Will he lose his civilization, or will he adapt by learning? Carrel seems to be intrigued by the question of what effect man's diet has upon his activity and his history. He wonders what peoples ate who achieved heroic and historic things in the past.

Repeatedly in the book he comments on the increasing complexity of our knowledge, and feels that this is only apparent and probably due to the deficiency of the means at our disposal for observation. He feels that Nature at the bottom is fundamentally simple, but to our limited perceptions, seems as complex as does the elephant to the blind man.

His arguments urging asceticism have been much commented upon. Properly interpreted, his attitude on asceticism is not fanatic; it is merely reasonable in the face of the modern tendency toward excessive comfort and diversion. History has confirmed the fact that comfort, lack of discipline, and a multiplicity of stimuli, destroy the initative and capacity for hard work that is necessary to the human being for success in adaptation to environment and the survival of the species.

The book is not easy to read. Although the sentences are short, they are dogmatic, and they are packed full of meaning so that many a short sentence may have to be repeatedly reread before its full significance is carried on into the paragraph. Although finishing the book does not exactly leave one in a state of back-slapping optimism, it is nevertheless highly stimulating to thought; and it is to be hoped that it is the first of a series by awakening minds which will bring back to discipline a civilization that is rapidly approaching its zenith.

Miles J. Breuer, Lincoln, Nebraska.

"La Sécrétine." By Jean La Barre. Bibliothèque Scientifique Belge. Published by Masson & Cie., Editeurs, Paris, 1936, 272 pp. Price, 30 francs.

FOR several years, with the assistance of his numerous co-workers, Jean La Barre, who is a Professor in the University of Brussels, has studied the physiological and chemical properties of secretin extracted from the duodenal mucosa. According to his view secretin, which is liberated by the hydrochloric acid of the chyme when it enters the duodenum, possesses two properties, (1) that of stimulating the secretion of pancreatic juice, and (2) that of lowering the blood sugar level. Both are properties of one and the same chemical body. However, by special chemical methods the particular part of this chemical body that stimulates pancreatic secretion—namely, "secretin"—may be separated from the part which produces hypoglycemia, and to which La Barre gives the name of "incretin." "Purified secretin," having either a very insignificant or no effect on the blood sugar, has been obtained by many investigators (Mellanby, Still, Ivy, Agren and others). La Barre succeeded in obtaining from the duodenal mucosa a product which was practically devoid of any secretagogue properties, but which retained its ability to reduce the blood sugar. Two different methods were used by La Barre in separating "incretin" from "secretin." As a source of "incretin" he employed a crude secretin extracted with a 0.5 per cent solution of HCl from hog's intestinal mucosa. One method was based on the solubility in ether of "incretin," precipitated from secretin by trichloracetic acid. However, a much better yield of "incretin" was obtained by the other method, namely, by the peptic hydrolysis of secretin obtained by precipitation with ammonium sulphate.

The physiological properties of "incretin" are as follows: It does not lower the blood pressure and is practically devoid of any secretagogue effect on the pancreas. Two to three hours after the intravenous administration of "incretin" in doses of from 5 to 10 mg. per Kg. body weight in a rabbit or dog, the blood sugar falls to a convulsive level. In contradistinction to insulin "incretin" may produce a hypoglycemic effect on being introduced through the mouth. For oral administration a dose of "incretin" three times larger, *i.e.* 15 to 30 mg. per Kg. body weight, is required in order to produce a marked fall of the blood sugar level. The maximum effect is reached in about four hours. The hypoglycemic action of "incretin" is of a double nature: (1) it stimulates the secretion of insulin, as was proved by the method of cross-circulation in two dogs, and (2) it has a direct hypoglycemic property, because it lowers the blood sugar level in depancreatized animals. La Barre succeeded in keeping depancreatized dogs in good health for several weeks by administering to them daily by mouth 30 mg. of "incretin" per Kg. body weight. "Incretin," like insulin, increases the deposition of glycogen in

the liver, and diminishes the glucose content of the venous blood of muscle. It increases the motility of the stomach and the secretion of gastric juice.

La Barre, in ten cases of human diabetes, studied the effect of "incretin" introduced by mouth in daily doses of from 0.5 to 1.0 gm. In mild cases of diabetes (hyperglycemia, 0.26 per cent; glycosuria, 0.57 per cent; traces of acetone in urine) such doses of "incretin" were sufficient to reduce the blood sugar to 0.14 per cent and abolish the glycosuria and acetonuria. In more severe cases of diabetes (hyperglycemia, 0.33 per cent; glycosuria, 1.4 to 1.3 per cent) after five days' treatment with 1 gm. of "incretin" the hyperglycemia showed a decrease, the blood sugar being reduced to about 0.13 per cent, and the glycosuria was diminished to 0.1 per cent. However, while "incretin" may be useful in mild cases of diabetes, La Barre believes that in severe cases of the disease it is advisable to combine "incretin" with insulin, because "incretin" performs two functions—it stimulates the endocrine function of the pancreas and it acts directly on the tissues, enabling them to assimilate carbohydrates.

Besides a thorough exposition of the facts relating to the hypoglycemic effect of secretin, the book contains a wealth of other information concerning secretin, as well as the different methods of preparing it and its physiological action on different organs. The book is written in a lucid style and the facts are clearly set forth, so that it makes very pleasant reading. Every quotation is accompanied by a reference to its source in the literature. There is an index both of authors and subjects.

It seems to the present reviewer that the appearance of Professor La Barre's book is most timely. It establishes an important relationship between the gastro-intestinal tract and one of the fundamental functions of the body, namely, the utilization of carbohydrate—a type of bodily relationship comparable to that existing between the secretory function of the gastric mucosa and the hematopoietic organs. This book contains a useful lesson for those who are inclined to minimize the importance of the gastro-intestinal tract in the general economy of the body, regarding it merely as a kind of test-tube in which the ingested food is prepared for absorption.

B. P. Babkin, Montreal, Canada.

Digestion and Health. By Walter B. Cannon. Published by W. W. Norton & Co., New York, 1936, 160 pp. Price, $2.00.

IN this admirably written little book Professor Cannon discusses the relation of digestion to health. His treatise is based chiefly on the work performed by himself and his numerous co-workers. In the four chapters which form the main body of the text the author discusses: I. The nature of appetite and hunger; II. The nature of thirst; III. Digestion and bodily vigor; IV. Indigestion from pain, worry and excitement. There are also an Introduction and an Epilogue. Although the medical reader will doubtless be familiar with Cannon's theories concerning the peripheral origin of hunger and thirst sensations, the nervous regulation of gastro-intestinal motility and the "emergency" theory of adrenin secretion, he will find that the book records a great many new observations and experiments and that the author displays a profound understanding of the whole subject. The volume represents, in an expanded form, the lecture delivered by the author to the Wayne County Medical Society on the occasion of the centenary celebration in 1933 of the publication of William Beaumont's famous book, "Experiments and Observations on the Gastric Juice and the Physiology of Digestion" (Plattsburg, 1833). I am sure that practitioners will read Professor Cannon's book with delight and with great profit. Moreover doctors would do well to recommend it to patients suffering from gastro-intestinal ailments, for the sick man could thereby acquire a better understanding of the important part played by the alimentary canal in the whole economy of the body. In many cases this book would undoubtedly be more beneficial to the patient than any medicine.

B. P. Babkin, Montreal, Canada.

Program of the Fortieth Annual Meeting of the American Gastro-Enterological Association

JUNE 7TH AND 8TH, 1937

HOTEL CLARIDGE, ATLANTIC CITY

MONDAY, JUNE 7, 1937

MORNING SESSION, 9:15 A. M.
Daylight Saving Time

MEMORIAL ADDRESSES

of

Henry Plummer by George B. Eusterman
Sidney Simon by Daniel N. Silverman
Frank Smithies by Clement Jones

PRESIDENTIAL ADDRESS

Chester M. Jones, Boston, Mass.

1. The Influence of the Extrinsic Innervation on the Human Gastric Motor Mechanism
   Louis E. Barron, New Haven (by invitation)
2. Experimental Studies in Gastric Physiology in Man. V. Influence of Osmetic Tension in the Duodenum on Pyloric Action and Gastric Evacuation
   Harry Shay and (by invitation) J. Gershon-Cohen, Philadelphia
3. A Theory on the Formation of Peptic Ulcer
   Heinrich Necheles, Chicago

4. Massive Hemorrhage from Peptic Ulcer
   John M. Blackford, Seattle

5. Hemorrhagic Gastritis: A Gastroscopic Study
   Edward B. Benedict, Boston (by invitation)

THE ALVAREZ LECTURE

Founded in 1929 by Dr. Frank Smithies

The Differential Diagnosis of Cardiac and Gastro-Intestinal Disorders
Paul D. White, Boston

Adjournment for Luncheon

2:30 P. M.

6. Cinefluorographic Studies of Lesions of the Gastro-Intestinal Tract
   DeWitt Stetten and William H. Stewart, New York

7. The Interdependence of Gastric Secretion and the CO_2 Content of the Blood and its Significance in the Alkali Treatment of Peptic Ulcer
   Everett D. Kiefer, Boston

8. Observations on Gastric Acidity Before and After Development of Gastric Carcinoma
   Mandred W. Comfort, Winfield L. Butsch (by invitation) and George B. Eusterman, Rochester, Minn.

9. The Psycho-biological Approach to Gastro-Intestinal Disorders
   Kenneth J. Tillotson, Cambridge, Mass. (by invitation)

EXECUTIVE SESSION

(Associate members are requested not to attend)

ANNUAL DINNER, 7:30 P. M.

HOTEL CLARIDGE, ATLANTIC CITY, N. J.

Guest of Honor

Kirkley F. Mather

Professor of Geology, Harvard University

"A Geologist in Prophetic Mood"

TUESDAY, JUNE 8, 1937

MORNING SESSION, 9:30 A. M.

10. Ulcer Recurrences Attributed to Upper Respiratory Tract Infections: A Possible Illustration of the Shwartzman Phenomenon
    Burrill B. Crohn and (by invitation) Gregory Shwartzman, New York

11. Studies in Mucous Membrane Hypersensitiveness. III. The Allergic Reaction of the Rectal Mucous Membrane after Passive Sensitization
    Irving Gray and (by invitation) Matthew Walzer, Brooklyn

12. Secondary Effects of Radiation Upon the Rectum Following the Treatment of Extrarectal Pelvic Lesions
    L. K. Ferguson, Philadelphia

13. Deficiency States Associated with Gastro-Intestinal Diseases
    Dwight L. Wilbur and Albert M. Snell, Rochester, Minn.

14. The "Diarrhea of Diabetes" and Steatorrhea of Pancreatic Insufficiency
    J. Arnold Bargen and (by invitation) Jesse L. Bollman, Edwin J. Kepler, Rochester, Minn.

15. The Diagnosis and Treatment of Acute Non-Hemorrhagic Pancreatitis
    Robert Elman, St. Louis

Adjournment for Luncheon

2:00 P. M.

16. Back Pain in Relation to Ulcers and other Gastro-Intestinal Disturbances
    W. Jason Mixter, Boston (by invitation)

17. Silent Renal Pathology Presenting Gastro-Intestinal Symptoms
    Alexander Randall and Boland Hughes, Philadelphia (by invitation)

18. Quantatative Studies on the Absorption of Glucose from the Human Small Intestine
    William O. Abbott, Walter G. Karr, T. Grier Miller, Philadelphia

19. Deposition of Glycogen in Normal and in Experimentally Damaged Livers After Oral and Intravenous Administration of Dextrose
    Theodore L. Althausen, San Francisco

20. Studies on Motility of the Colon
    A. J. Carlson, Chicago

The following papers will be Read by Title:

The Effect of Histamine on Gastric Secretion
Leon Schiff, Cincinnati

Report of a Case Showing a Relationship Between the Irritable Colon Syndrome and Upper Intestinal Dysfunction
Edward S. Emery, Jr., Boston

Abstracts

FELSEN, JOSEPH.

Acute and Chronic Bacillary Dysentery. Am. Jour. Path., XII, 3, p. 395, May, 1936.

A study based primarily upon the Jersey City epidemic of bacillary dysentery of 1934 is presented. The author's main purpose has been (1) to stress the fact that acute bacillary dysentery is a systemic disease in which the pathological lesions are caused by one or more toxins affecting, as well, extra-enteric organs; that the intestine alone need not bear the main brunt of the infection; and (2) that the late manifestations of the disease bear a very close relationship to non-specific ulcerative colitis.

It is believed that the intestinal lesions in the human are due to the excretion of the dysentery toxin, circulating in the blood stream, through the bowel wall. It is believed, too, that the toxin may be reabsorbed and repeat the cycle. The terminal ileum and colon seem to have a predilection for the toxin as the greater lesions are found there, although any portion of the bowel may be involved. An enteric and a neurotropic toxin have been isolated by Olitsky and Kligler. Clinical evidence exists which points to the presence of an arthritic and a myelotropic toxin also. The frequent association of labial herpes suggests, too, the presence of a virus. Examinations of the spinal fluid and the fluid from joints have failed to show the presence of microorganisms. In the chronic type of disease with arthritis, the acute dysentery infection having long before subsided, the joint involvement is probably due to a streptococcus or streptococcic toxin. The enterococcus is often recovered from the stools and other materials. A marked toxic granulocytopenia is at times observed. As the bone marrow in two cases coming to autopsy showed no evidence of deficiency in granulocyte formation, it was concluded the destruction of the leucocytes took place in the peripheral blood or in the vascular sinusoids of the bone marrow into which the granulocytes must migrate after their extravascular formation. Therefore the toxins of B. dysenteriae should be considered from the standpoint of selectivity as enteric, neurotropic, arthritic, and myelotropic. The Shiga-Kruse, Flexner, Hiss and Sonne-Duval strains all enter into the general picture.

The intestinal lesion in the acute dysentery begins as a definite hyperemia of the mucosa of large and small intestine with moderate edema and diffuse lymphoid hyperplasia of the solitary acuminate lymph nodules. Peyer's patches are similarly involved. The goblet cells pour out quantities of mucus, apparently for protection. On the second and third days blood oozes through the relatively intact epithelium. Superficial mucosal ulceration takes place—the lymph nodes become larger and central necrosis appears. The mild case usually does not extend beyond this stage. As the terminal ileum is severely affected patients have been on occasion operated upon for acute appendicitis—the mesenteric lymph nodes are then seen to be large, soft and pinkish in color. The acute stage usually subsides by the end of the third week. Continuing intestinal symptoms indicate chronicity and probably secondary non-specific intramural infection. The mucosa bleeds easily on examination, ulcers appear, and, as time goes on, the submucosa and deeper layers become involved, the wall thickened, haustration eliminated, pseudopolyposis may occur, etc.—the picture of chronic ulcerative colitis.

Follow up studies of cases of acute bacillary dysentery have shown that in some patients intestinal lesions persist long after the dysentery organism has disappeared from the feces. The longest period of observation was 4 years. In the Jersey City epidemic 122 cases out of a total of 210 hospitalized patients were examined 9 to 12 months after the acute attack; 18.8 per cent gave evidence of chronic ulcerative colitis. Epidemiological studies revealed definite contact and familial incidence in non-specific ulcerative colitis and a geographic districution corresponding to that of bacillary dysentery. Positive agglutination titers against B. dysenteriae were obtained in 62 consecutive cases of non-specific ulcerative colitis, in 2 of non-specific granuloma, and in 14 cases of chronic distal ileitis. Control studies of 300 serums showed diagnostic titers in 4.6 per cent.

The laboratory diagnosis depends upon: 1. fecal culture,—the specific dysentery organism is often isolated only during the first week; 2. diagnostic fecal bacteriophage; and 3. agglutination titer. The second begins to appear in the feces and the agglutination titer to rise in the blood after this time.

The character and modification of the dysentery toxins suggest that to be effective therapeutically, a specific serum must be used within the first few days when the major intestinal lesions occur. It should be an anti-toxin effective against known toxins that have been properly standardized by biological methods. Active immunization must be directed chiefly against the secondary non-specific invaders.

N. W. Jones, Portland, Oregon.

COLE, L. G.

The Pathological Yardstick. Its Accuracy as an Instrument for Measuring Errors in Clinical, Roentgenological, and Surgical Diagnosis of Gastric Lesions. S. G. O., Vol. 63, No. 6, pp. 689-716, Dec., 1936.

The author secured eight microscopic sections from seven organic gastric lesions and presented them to a group of representative and outstanding pathologists. Each pathologist was asked to state positively whether the lesion were a malignant one, and the type of malignancy if it were considered so. The criteria for each opinion were obtained for most of the pathological diagnoses given. If the pathologist were engaged in teaching, he was asked whether he would pass a student who could not differentiate a malignant lesion from a benign one. The answers to that question are not included in the paper.

In the answers received there was an incomprehensible diversion of pathologic opinion. In the study of some sections the pathologists were nearly equally divided in their opinions as to whether the lesion were malignant or benign. Among those who considered a particular lesion to be malignant there were some who diagnosed it as carcinoma, other diagnosed sarcoma, while others diagnosed lymphosarcoma. There was no unanimity of opinion concerning any one section. Of two sections made from the same specimen one was considered malignant by a large majority of the pathologists, while the other was considered benign by an equally large majority.

Certain of the pathologists when confronted with the results of this study made various remarks. Ewing under such circumstances remarked that there is no sharp line of demarcation between benign and malignant lesions. The author regards that as Ewing's most important and significant report.

The author believes that in studying a given section all the pathologists do not look at the same minute details of the section, others compare it to things they have seen before. Certain details do not mean the same thing to every pathologist and certain words have quite different meanings to different pathologists. Different lighting conditions and the degree of individual fatigue at the time the study is made are other factors which contribute to the truly incomprehensible diversion of pathologic opinion.

From this study the author has gathered a number of criteria by means of which neoplastic processes may be

differentiated from inflammatory ones. These will be reported at a future date. The effect of this difference of opinion among pathologists on the statistics of "surgical cures" and numerous other studies is obvious.

Eleven figures, three tables, a detailed account of each case, and each pathologists report accompany the article.

Nelson M. Percy, Chicago.

RIGLER, LEO G.

Leukemia of the Stomach Producing Hypertrophy of the Gastric Mucosa. J. A. M. A., Vol. 107, pp. 2025-2029, Dec. 19, 1936.

Generalized leukemic infiltration of the viscera, as well as of the bones, is not uncommon. Frequently it occurs with an aleukemic blood picture which may later change to a true leukemia.

The roentgen interpretation of this and similar conditions is bizarre, but exceedingly difficult to diagnose. The stomach usually shows a localized infiltration, often near the pylorus, with a marked constriction of the lumen of the stomach. There is also in many cases an elevation of the gastric mucosa throwing the rugae into large folas resembling the gyri of the brain.

The author presents two cases which roentgenologically resembled the above description but only one of them had characteristic findings of leukemia and responded to roentgen irradiation. He reached the conclusion that leukemia will produce a roentgen picture which is difficult to distinguish from other lesions, but which will change, or respond, to roentgen treatment.

Francis D. Murphy, Milwaukee.

DECOURCY, JOSEPH L.

Care of the Ruptured Appendix. Reduction of Mortality to Four Per Cent in Series of Fifty Cases. S. G. O., Vol. 63, No. 6, pp. 756-760, Dec., 1936.

The author quotes various statistics on the mortality of acute appendicitis showing how the mortality has increase from approximately 7 per 100,000 persons in 1900 to approximately 14 per 100,000 persons in 1933. He feels that this is not an entirely correct representation of the real truth.

Two avenues to lower the mortality of acute appendicitis are open to us: (1) the continuous and increasingly vigorous education of the public to the dangers of procrastination; (2) improved technical handling of the ruptured cases. Along the first avenue the need is obvious and well known.

It is along the second avenue that the author suggests an improvement. In a series of 50 cases of appendicitis with perforation, the author inserted a Pezzer catheter into the cecum after removing the appendix. That has served to decompress the colon, and has been useful as a means of instilling fluids into that part of the intestinal tract from which they are most readily absorbed. Later enemas and flushings of the bowel may be given through this catheter. The catheter usually begins to drain within twenty-four hours, and continues for 4 to 5 days. After the bowels act naturally the drainage from the catheter diminishes. The author does not state just when it is removed. Continuous gastric lavage by the continuous method as devised by Wangensteen is employed in certain cases. In this series of 50 cases the mortality was 4 per cent.

The author prefers the right rectus incision to the McBurney incision because it allows better access to the pelvis. In cases of appendiceal abscess the author feels strongly that any operation that does not remove the appendix is only a palliative measure and invariably invites sequels. By enlarging the incision, and carefully packing off the intestines, the appendix may be removed and the wound closed with or without drainage as the case may require.

The author believing that death in cases of ruptured appendicitis is due more to distention from intestinal obstruction than to infection, is of the opinion that the use of the Pezzer catheter will relieve the distention and lower the mortality of that condition.

Nelson M. Percy, Chicago.

GLENN, F.

Gastro-enterostomy. A Detailed Description of One Surgical Procedure. S. G. O., Vol. 63, No. 6, pp. 751-755, Dec., 1936.

The author presents in detail a method of making a gastro-enterostomy which, he hopes, will stimulate discussion which in turn will be followed by some progress in that field of surgery.

Pre-operatively the patient is fed on a high caloric diet and dental hygiene is instituted. The stomach is emptied twice daily in order to restore the normal elasticity of its walls and to reduce the number of bacteria in its contents.

The operative technique is the one originally described by Halsted. No clamps are used; all vessels are ligated with fine plain catgut. The opening through the mescolon should be to the left of the middle colic artery when possible. The site of the anastomosis on the stomach should be along an oblique line on the posterior surface of the prepyloric region. It should measure 10 centimeters in length. In selecting the site of anastomosis on the jejunum two points must be considered. The arrangement must be iso peristaltic and the loop of jejunum above the anastomosis must be long enough to prevent tension, yet not long enough to allow puddling of its contents. The proximal end of the stoma should be 10-15 centimeters from Treit's ligament. Silk sutures are used for the approximation of the serosa; No. 1 plain catgut is used as a suture through the entire thickness of the wall of the stomach and jejunum. The transverse mesocolon is attached to the gastric side of the anastomosis by means of interrupted silk sutures.

Postoperatively saline is given subcutaneously and glucose intravenously. Inhalations of carbon dioxide are given every two hours. If the patient is anemic a small blood transfusion may be given. The fluid intake is maintained at about 3000 c.c. daily. Nothing is given by mouth during the first two days, then small amounts of water and later albumin water, coddled egg and buttermilk are given. At the end of two weeks the patient eats a full variety of foods.

Postoperative vomiting may be controlled by gastric lavage. Pulmonary complications are avoided by frequently changing the position of the patient. It at the end of the second week the stoma is not functioning, operative correction of the fault may be necessary.

Six figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

DR. RIESMAN HONORED

Dr. David Riesman was guest of honor at a dinner on the evening of March 25, 1937, at the Bellevue-Stratford, Philadelphia, attended by more than 250 of his professional friends on the occasion of his seventieth birthday. Guest speakers included: Provost Josiah Penniman, Dr. Alfred Stengel, Dr. Henry A. Christian, Dr. Lewis A. Conner, Dr. Wilmer Krusen, Dr. William Gerry Morgan and Dr. Walter C. Alvarez. Dr. Russell Boles was toastmaster. Dr. Stanley C. Harris announced that friends of Dr. Riesman had made possible the publication of a volume of his selected writings to celebrate his birthday. An engraved plate, bearing the names of Dr. Riesman's former and present assistants, was presented by Dr. Thomas Fitz-Hugh, Jr. Dr. Riesman responded with a characteristically delightful account of his medical career and of his view of the present and future of medicine envisioned from the vantage point of his 'seventy year-high mountain-top."

SURGEONS WILL TAKE SCANDINAVIAN TOUR

New York, April. The Society of Clinical Surgeons, following their time-honored tradition of taking a trip abroad approximately every five years, will pay their first visit as a Society to Scandinavia this July. They have invited members of the Interurban Surgical Society, with their families, to join in the tour and the two groups will sail July 2 under Cook's auspices on the S. S. Gripsholm. They will visit the outstanding clinics of Denmark,

Sweden and Norway, which have been attracting much attention in recent years, and will combine scientific interest with the recreational and sightseeing features of a holiday abroad, continuing on to England and Scotland before returning to the United States.

The Society of Clinical Surgeons visited Great Britain in 1910, Germany in 1912, France, Italy, Austria and the Netherlands in 1925, and the British Isles again in 1930. This summer's Scandinavian Tour will cover Gothenburg, Copenhagen, Stockholm, Oslo, Ulvik, Stalheim, Voss and Bergen. Proceeding thence by steamer to Newcastle, the Society will round out its trip with visits to London, Edinburgh, the Trossachs and Glasgow, arriving in New York via the S. S. Caledonia, August 16.

Cook's conducted a similar trip last year for the Southern Society of Clinical Surgeons.

Preliminary Program of the Thirty-Eighth Annual Meeting of the American Proctologic Society

ATLANTIC CITY

Sunday, Monday and Tuesday, June 6, 7, 8, 1937

Headquarters: The Marlboro-Blenheim

Admission to the annual meetings is confined to members and such guests as are sponsored by members and thereafter invited by the Executive Council.

TENTATIVE SUMMARY OF EVENTS

SUNDAY, JUNE 6th—

Registration, The Marlboro-Blenheim	10:00 A.M.
Entertainment	2:00 P.M.

MONDAY, JUNE 7th—

Registration	8:00 A.M.
First Scientific Session	9:00 A.M.
Luncheon	12:00 Noon
Second Session	2:00 P.M.
Executive Session (for Fellows only)	8:00 P.M.

TUESDAY, JUNE 8th—

Third Scientific Session	8:00 A.M.
Luncheon and Round Table Conference	12:00 Noon
Fourth Session (Cancer Symposium)	2:00 P.M.
Annual Society Dinner (The Marlboro-Blenheim)—All registered guests invited	8:00 P.M.

WEDNESDAY, JUNE 9th—

AMA Section on Gastro-enterology and Proctology begins 3-day session	9:00 A.M.
AMA Section Dinner (The Marlboro-Blenheim) — All proctologists invited	7:30 P.M.

THE SCIENTIFIC PROGRAM—(Tentative)

Presidential Address: Problems and Progress of the American Proctologic Society. Dr. Marion C. Pruitt, Atlanta, Georgia.

Report of Committee on Arrangements: Dr. Homer L. Silvers, Atlantic City.

Memorial to Dr. Synott: The Secretary.

Review of the Literature of 1936: Dr. Warren R. Rainey, St. Louis, Mo.

CASE REPORTS

(Speakers are allotted five minutes and there is no discussion)

Ovarian Carcinoma Simulating Rectal Cancer: Dr. Martin S. Kleckner, Allentown, Pa.

Portable Sitz Bath for Rectal Cases: Dr. Cecil D. Gaston, Birmingham, Ala.

Rupture of the Intestinal Canal with Compressed Air: Dr. C. C. Neese, Wilmington, Delaware.

Tuberculosis of the Lungs, Cecum and Anus: Dr. Homer H. Wheeler, Indianapolis, Ind.

Neurofibroma of the Rectal Wall: Dr. Albert R. Keith, Hartford, Conn.

Diathermy Dilators for Rectal Stricture: Dr. F. M. Frankfeldt, New York City.

Adenocarcinoma of the Anus: Dr. Valentine R. Manning, Philadelphia, Pa.

Diverticulum of the Rectum with Fecal Impaction: Dr. Meyer H. Freund, New York City.

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Uterine Sarcoma: Dr. Julius L. Werner, Philadelphia, Pa.

FORMAL PAPERS (15 Minutes)

Ileo-Colitis: Dr. Burrill B. Crohn, New York City. (By invitation).

The Place of Proctology Among the Surgical Specialties: Dr. M. S. Wolff, San Francisco. Discussion: Dr. Collier F. Martin, Philadelphia.

Perineal Hernia: Dr. Frank C. Yeomans, New York City. Discussion: Dr. Deseum C. McKenney, Buffalo.

Cod Liver Oil per Rectum as an Adjunct in the Treatment of Chronic Ulcerative Colitis: Dr. R. Russell Best, Omaha, Neb. Discussion: Dr. Walter A. Bastedo, New York City.

The Supra Levator Abscesses: Dr. H. Z. Hibshman, Philadelphia, Pa. Discussion: Dr. Louis J. Hirschman, Detroit.

Roentgen Aid to a Proctologic Diagnosis: Dr. C. C. Mechling, Pittsburg, Pa. Discussion: Dr. Alois B. Graham, Indianapolis.

The Management of Strangulated Hemorrhoids: Dr. Emor L. Cartwright, Fort Wayne, Ind. Discussion: Dr. Walter L. Fansler, Minneapolis.

Endometriosis of the Rectum and Sigmoid: Drs. James Schofield and Harry E. Bacon, Philadelphia, Pa.

SYMPOSIUM ON ANESTHESIA

Intravenous Anesthetic Agents in Proctology: Dr. Benjamin Haskell, Philadelphia, Pa.

Rectal Operations Under Local Anesthesia: Dr. Joseph H. Saphir, New York City.

Oil Soluble Anesthetics in Ano-Rectal Surgery: Dr. W. W. Green, Toledo, Ohio. Discussion: Dr. Marion S. Pruitt, Atlanta, Ga. Dr. F. B. Bowman, Hamilton, Canada. Dr. A. G. Carmel, Cincinnati, Ohio.

THE SYMPOSIUM ON CANCER OF THE RECTUM AND COLON

The Diagnosis of Rectal and Colonic Cancer: Dr. William H. Daniel, Los Angeles, Calif.

Selected Methods in the Treatment of Rectal Cancer: Dr. George E. Binkley, New York City.

The Treatment of Adenocarcinoma of the Rectum by Dessication: Dr. Edward G. Martin, Detroit, Mich.

Colectomy for Polyposis and Cancer of the Colon: Dr. Robert Scarborough, San Francisco, Calif.

The Rationale of the Surgical Technique in Carcinoma of the Rectum and Sigmoid: Drs. Jerome M. Lynch and G. Johnson Hamilton, New York City. Discussion: Dr. Louis A. Buie, Rochester, Minn. Dr. Thomas E. Jones, Cleveland, Ohio. Dr. Dan Jones, Boston, Mass. Dr. Dudley Smith, San Francisco, Calif.

Curtice Rosser, M.D., F.A.C.S.
710 Medical Arts Bldg.,
Dallas, Texas.

INTERNATIONAL CONGRESS ON HEPATIC INSUFFICIENCY

While the Universal Exhibition is being held in Paris, the International Congress on Hepatic Insufficiency will be in session at Vichy on the 16th, 17th and 18th of September, 1937, under the presidency of a member of the Academy of Medicine, Prof. Maurice Loeper of Paris. It will be divided into two sections:

(1) Medicine and Biology

(2) Medical, Surgical and Hydrological Therapy

Papers will be submitted in the two sections by the following gentlemen of different countries:

Medicine and Biology: K. Glaessner (Vienna): The Functional Diagnosis of Hepatic Insufficiency.

R. Debre, Gilbrin, Semelaigne (Paris): Enlarged Liver in Children.

Binet (Paris): The Sulphur Function of the Liver. The Edema Associated with Liver Dysfunction.

Lemaire and Varey (Paris): Pathogenical Study and J. Olmer (Marseilles): Clinical Study.



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Urbach (Vienna): The Skin and the Liver.

Parhon (Bucharest): The Liver and the Endocrine Glands.

Hamilton Fairley (London): The Stages of Hepatic Insufficiency in the Course of Malaria.

Therapy: Lathan A. Crandall (Chicago), A. C. Ivy (Chicago), Anthony Bassler (New York City), Norman Elton (Reading) and Hyman I. Goldstein (Camden): Hepatic Insufficiency in its Relations to General Nutrition and Especially to the Nervous System.

M. Brule (Paris): Hepatic Medications in Cases of Intolerance.

M. Villaret, L. Justin-Besancon, R. Cachera and R. Fauvert (Paris): Circulatory Insufficiencies and their Medications.

Piery and Milhaud (Lyons): The Hydro-Mineral Therapy of Hepatic Insufficiency.

DeGrailly (Bordeaux): Cellular Insufficiency and its Therapeutic Indications.

Gallart-Mones (Barcelona): Diet in the Restoration of an Impaired Liver.

Pribram (Berlin): Pre-operatory and Post-operatory Hepatic Insufficiency and its Preventive and Curative Treatment.

P. Duval, Gatelier, J. C. Roux, Goiffon (Paris): The Prognostic of the "Operative Crisis" by the Examination of the Hepatic Functions.

It may be recalled that this Congress will be preceded by the Second International Congress on Gastro-enterology, to take place in Paris on the 13th, 14th and 15th, September, 1937, under the presidency of Prof. Pierre Duval, at which two questions will be discussed:

(1) The Early Diagnosis of Cancer of the Stomach, under the presidency of Profs. P. Duval and Gosset of Paris, and of Prof. Konjetzny of Berlin.

(2) Acute and Chronic Occlusion of the Small Intestine: Authors have been selected in England, Belgium, Spain, the U. S. A., Italy and Poland for papers dealing with this latter question.

Those desiring to attend these Congresses may receive information by applying to Dr. Anthony Bassler, 121 East 71st St., New York City.

1937 GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE

For the Annual Graduate Fortnight of The New York Academy of Medicine a subject of outstanding importance in the practice of medicine and surgery is selected and is presented from as many angles as possible. It offers to the profession a resume of the present knowledge of the subject so that the practitioner may be so informed.

The Tenth Annual Graduate Fortnight will be held November 1 to 12 and will be devoted to a consideration of Medical and Surgical Disorders of the Urinary Tract. The subject will include *Bright's disease, arterial* hypertension, and infections, tumors, calculi and obstructions of the urinary tract, and will exclude veneral disease, diseases of the genitalia and gynecology.

Twenty important hospitals of the City will present coordinated morning and afternoon clinics and clinical demonstrations. At the evening meetings prominent clinicians of New York and many of the other leading medical centers of this country who are recognized authorities in their special fields will discuss the several aspects of the general subject.

A comprehensive exhibit of books, pathological and research material, diagnosis, treatment and prevention whenever possible, clinical and laboratory diagnostic methods, X-rays, action of drugs and other therapeutic measures. Demonstrations will be held at regular intervals.

Some of the features to be presented



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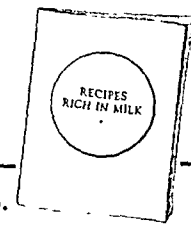
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* Journal A.M.A., March 20, 1937



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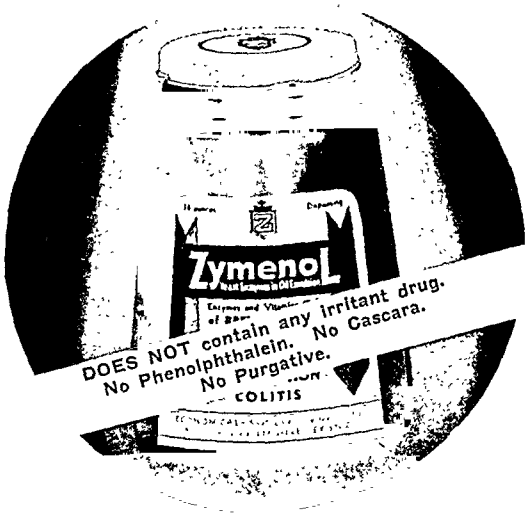
at the meetings, in the clinics and in the exhibit will be:

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Edema and its treatment
Uremia and pathology of kidney function
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Clinical aspects of nephritis including glomerular, focal, embolic and acute interstitial nephritis
Nature of hypertension
Clinical aspects of hypertension, including malignant hypertension
Evaluation of the surgical treatment of hypertension
The nephroses
Vascular and renal complications of pregnancy
The relation of psychogenic factors of hypertension
Pathogenesis and treatment of renal infections
Renal and perirenal infections
Tuberculosis of the kidney
Calculus disease. The formation of stones
Clinical aspects of calculus disease
Hydronephrosis and pyonephrosis
Bright's diseases in children
Common urologic diseases in children
Radiotherapy of tumors of the urinary tract
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The following list of abstracts throw light on the vitamin value of canned foods:*

KOHMAN, E. F., EDDY, W. H. AND CARLSSON, VICTORIA.

Vitamin in Canned Foods. II. The Vitamin C Destructive Factor in Apples. 1924, Ind. Eng. Chem., 16, 1261.

Best modern canning practices for apples, allow the fruit to stand for some time in a 2 per cent salt solution in order to permit the removal of oxygen by respiratory processes. Apples cooked without the removal of oxygen suffer large losses of vitamin C. The vitamin C content of apples canned after removal of oxygen, compared favorably with that of the raw fruit.

SHERMAN, H. C., LAMER, V. K. AND CAMPBELL, H. L.

The Quantitative Determination of the Antiscorbutic Vitamin (Vitamin C). 1922, J. Am. Chem. Soc., 44, 165.

Filtered tomato juice, prepared from commercially canned tomatoes was used as the source of vitamin C in the experimental work. No symptoms of scurvy were found in guinea pigs receiving 3.0 ml. of this juice daily, as the sole source of vitamin C. It is concluded that commercially canned tomatoes are an excellent source of the antiscorbutic vitamin.

KOHMAN, E. F., SANBORN, N. H., EDDY, W. H. AND GURIN, CELIA ZALL.

Vitamins in Canned Foods. XIV. Calcium and Vitamin D in Foods. Ind. Eng. Chem., 26, 758, 1934.

Rats were carried through five generations on the following diets: a mixture of raw foods, the same mixture home cooked, and a similar mixture of

*These abstracts were furnished by the Research Department of the American Can Company. *Editor.*

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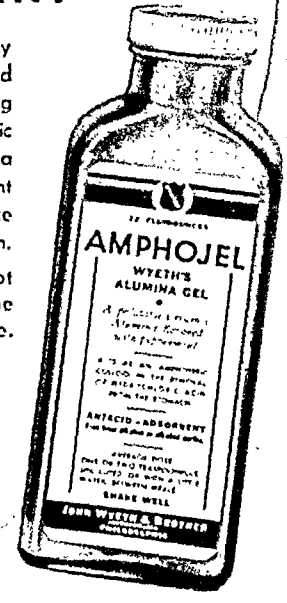
Amphojel, Wyeth's Alumina Gel, is a creamy palatable colloidal suspension of hydrated alumina—$Al_2(OH)_6$—capable of neutralizing in one hour not less than 12 volumes of gastric juice containing 0.36% hydrochloric acid. Thus, a teaspoonful will neutralize to Toepfer's reagent over one and one-half fluid ounces of such juice or a corresponding amount of stronger secretion.

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commercially canned products. With rate of growth, weight of young at birth and weaning, number of deaths before weaning, and per cent ash of the tibia used as the means for comparison, the canned food diet was found to be superior to either the raw or home cooked diet.

The addition of milk or calcium salts to a mixture of five common foods produced an increase in ash content of the tibia. Addition of cod liver oil to a diet of canned foods, along with calcium salts added to give the calcium phosphorus ratio of the Steenbock rachitogenic ration, did not produce a further increase in bone ash.

Experiments reported by the authors demonstrate that ordinary foods contain a significant amount of vitamin D, and that most foods are deficient in calcium. The better performance of rats on the canned food diet was believed to be due to a greater availability of a limited calcium supply.

WHEELER, G. A.

The Pellagra-Preventive Value of Autoclaved Yeast, Canned Flake Haddock, and Canned Green Peas. U. S. Public Health Reports, 48, 67, 1933.

The food studied was fed as a supplement to a basic diet which was known to produce pellagra in the human. Regular commercial products were used in these studies.

Canned flake haddock at the rate of 227 grams daily did not prevent the occurrence of certain symptoms of pellagra. Daily portions of 340 grams protected women from all traces of this disease. These findings demonstrate the value of canned haddock in the prevention of pellagra.

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DEVANEY, GRACE M. AND PUTNEY, LYDIA K.

The Vitamin A and D Content of Canned Salmon. J. Home Econ., 27, 658, 1935.

Two to four brands each of Chum, Pink, Red, and Chinook salmon purchased on the retail market, were examined for vitamin A and D potency. The liquid in the cans as well as skin and bone were removed before feeding. The vitamin A and vitamin D contents of the various brands expressed in International units are given in the following table:

Vitamin Content of Salmon

Variety	International Units of Vitamin A per Gram	International Units of Vitamin D per Gram
Chinook	8	3.9
	4	2.6
		2.1
Red	4	8
	2.5	
Pink	1	7.1
	1	7.8
		6.2
		4.0
Chum	0.5	2.6
		1.9

These data indicate that Chinook and Red salmon are richest in vitamin A. Red and Pink varieties are the best sources of vitamin D. Of the foods commonly included in the diet, canned salmon is one of the richest sources of vitamin D. In addition to vitamins A and D canned salmon supplies an inexpensive protein of excellent biological value.

EDDY, W. H., GURIN, CELIA ZALL AND KOHMAN, E. F.

Vitamins in Canned Foods. XII. Supplementary Nature of Grapefruit and Prunes. Ind. Eng. Chem., 24, 457, 1932.

The vitamin C contents of raw and canned grapefruit were compared by means of guinea pig feeding tests. Three grams per day of either the fresh or canned fruit fully protected guinea pigs from scurvy, and only mild symptoms of scurvy were found in guinea pigs receiving a two gram dosage.

Hepatic Lesions Presumably Secondary to Pancreatic Lithiasis and Atrophy; Report of Two Cases

By

ALBERT M. SNELL, M.D.*

and

MANDRED W. COMFORT, M.D.*

ROCHESTER, MINNESOTA

PHYSIOLOGISTS have long been aware that depancreatized animals maintained with insulin and dietary regulation alone are liable to develop hepatic insufficiency due to infiltration of the liver with fat. Ivy, in a recent discussion of the physiology of the pancreas, raises the question whether such changes ever occur in human subjects and states that to his knowledge they have not been observed. We have recently had under observation a young man with pancreatic lithiasis, diabetes mellitus, and steatorrhea which has been proved to be due to complete absence of the external pancreatic secretions; he apparently has complete, or nearly complete, pancreatic insufficiency. His case is of particular interest because of the late and rather sudden development of secondary changes in the liver which are presumably comparable to those which have been described in the experimentally pancreatectomized animal. In addition, two other patients with chronic pancreatic disease have been seen at the clinic, apparently with similar changes in the liver. We propose to report these cases and to summarize the available information on the subject of hepatic lesions which may be secondary to pancreatic disease.

The usual sequelae of pancreatectomy in the dog are well known and require only brief consideration. Fisher (1924) was the first to show that while pancreatectomized dogs could live as long as eight months with insulin and dietary care, all of them succumbed eventually to a condition other than diabetes. The usual, and often the only, postmortem finding of significance was marked enlargement of the liver with an extreme degree of fatty degeneration. Allan, Bowie, MacLeod, and Robinson published a report which confirmed Fisher's findings in the same year, noting that shortly after pancreatectomy there was deposition of fat in the liver, which cleared under treatment with insulin, and that a second fatal episode of fatty degeneration which was unaffected by dietary regulation or insulin occurred later in the course of the experiment. At necropsy of some of these animals the liver was found to contain as much as 20 per cent fat by weight. When raw pancreas was added to the diet, fatty change in the liver was to a great extent prevented.

In 1932, Best and Hershey reported their studies on the subject, especially from the standpoint of the effect of fatty degeneration of the liver on carbohydrate metabolism. When hepatic insufficiency developed in their animals, weakness, loss of weight and anorexia were the first symptoms; the dogs later became slightly jaundiced and glycosuria diminished gradually on a constant diet, so that, finally, little or no sugar was found in the urine. If lecithin was added to the diet, it was found that it prevented fatty deposition and maintained the animals in good condition; biopsy specimens of the liver did not contain deposits of fat, while glycosuria was increased to its original level. Later (1933), Best, Ferguson, and Hershey demonstrated by direct and indirect methods that choline, an important component of lecithin, also prevented the deposition of fat in the liver. Dragstedt and his associates (7, 15) (1936) have reported their studies on the relation of pancreatic activity to fat metabolism. They showed that fatty degeneration of the liver is not primarily due to loss of pancreatic secretions in the digestive tract and that the condition is not relieved by the oral administration of pancreatic juice. They have demonstrated further that the pancreas contains a substance which on administration by mouth prevents the deposition of fat in the livers of pancreatectomized dogs. This substance, which they have named "lipocaic," is presumably a hormone with a regulatory effect on the deposition and metabolism of fat.

If these studies on animals can be applied clinically, it seems reasonable to suppose that fatty degeneration of the liver might develop when there was sufficient pancreatic damage to produce more or less complete pancreatic insufficiency, and that the process might reasonably be expected to respond to the administration of lipocaic. We believe such a condition existed in our first case.

REPORT OF CASES

Case 1. The patient, a mechanic, aged thirty-six, was observed over a period of about two years. He was of reasonably good habits, but admitted that he drank to a moderate extent. At the age of twelve years he had had biliary colic followed by jaundice; no further details of this illness are available. At the age of twenty-eight he began to suffer attacks of severe upper abdominal pain which was projected bilaterally, more to the left than to the right, and which also extended to the back. Repeated injections of morphine always were necessary for relief. At the age of twenty-nine, abdominal exploration was performed because of the suspicion of a penetrating or perforating peptic ulcer; no ulcer was found but the operating surgeon noted induration of the pancreas. Between the ages of twenty-nine and thirty-six, the patient continued to have attacks of severe abdominal pain at frequent intervals, usually followed by vomiting and sometimes by diarrhea. Six weeks before the time of his first admission to the clinic in the spring of 1935, diabetes mellitus developed which was severe from the onset; about

*Division of Medicine, The Mayo Clinic.

Submitted March 16, 1937.

The Contents Of The June Journal Will Be As Follows:

HEPATIC LESIONS PRESUMABLY SECONDARY TO PANCREATIC LITHIASIS AND ATROPHY: REPORT OF A CASE - *Albert M. Snell, M.D. and Mandred W. Comfort, M.D.*

HYDROGEN PEROXIDE AS A DEPRESANT OF GASTRIC ACIDITY - *C. U. Culmer, B.A., A. J. Atkinson, M.S., M.D. and A. C. Ivy, M.D., Ph.D.*

A CONTRIBUTION TO THE ETIOLOGY OF GALL STONES - *Maurice Feldman, M.D., Samuel Morrison, M.D., C. Jeluff Carr, M.S. and John C. Krantz, Jr., Ph.D.*

PERISTALTIC RUSH STUDIED WITH NEW APPARATUS - - - - - - - - - - - - - - *Walter C. Alvarez, M.D.*

AN OFFICE PROCEDURE FOR THE RAPID ESTIMATION OF PEPSIN AND ITS CLINICAL SIGNIFICANCE - *Harry Barowsky, M.D., Henry Tauber, Ph.D. and Israel S. Kleiner, Ph.D.*

ABNORMALITIES OF THE ROTATION OF THE MIDGUT - - - - - - - - - - - - - - - *Gerhard Danelius, M.D.*

FURTHER REFINEMENTS IN THE METHOD OF ADMINISTERING COLON BACILLUS VACCINE THERAPY, AND IN THE THERAPEUTIC USE OF SODIUM RICINOLEATE - - - - - - *John G. Mateer, M.D., and James I. Baltz, M.D.*

INFANT FEEDING—INDIVIDUALIZED VS. ROUTINE - - - - - - - - - - - - - - *I. Newton Kugelmass, M.D.*

A CASE OF TRICHOMONAS HOMINIS INFESTATION - - - - - - - - - - - - - - - *Horace W. Soper, M.D.*

COLITIS ULCEROSAS GRAVES NO AMIBIANAS ETIOLOGIA, DIAGNOSTICA Y TRATAMIENTS MEDICO - - - - - - - - *F. Gallart Mones and P. Domingo Sanjuan. Abstract by J. Arnold Bargen, M.D. and Antonio E. Mendes Ferreira, M.D.*

CAUSES AND TREATMENT OF PEPTIC ULCER - - - - - - - - - - - - - - - - - *Paul Campiche, M.D.*

INTESTINAL MOTILITY IN RATS ANESTHETIZED WITH ETHER - - - - - - - - *George A. Emerson, M.S., Ph.D.*

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The vitamin C content of canned grapefruit, one of the best sources of this vitamin, is substantially that of the raw fruit.

Rats receiving 3 to 7 grams of raw or canned grapefruit as a source of vitamin A failed to grow. This fruit contains no appreciable quantity of vitamin A.

Raw and canned grapefruit contain both vitamins B and G in rather limited quantities. They appear to contain slightly more vitamin G than B.

The vitamins in grapefruit are apparently stable under the conditions existing in the commercial canning procedure.

CLOW, BERTHA, PARSONS, HELEN T. AND STEVENSON, INA.

The Vitamin C Content of Commercially Canned Sauerkraut Together with Some Observations on Its Vitamin A Content. J. Agr. Res., 41, 51, 1930.

Two brands of commercially canned sauerkraut were found to protect guinea pigs from scurvy if fed at the rate of 5.0 grams daily. This was the protective dosage found for a sample of raw sauerkraut. Four other brands of canned sauerkraut were found to be less potent sources of vitamin C. The least potent brand contained 1/3 to 1/2 as much vitamin C as the most potent brand. The six brands of sauerkraut examined were packed from different samples of cabbage and under different conditions; therefore, the factors responsible for the variations in vitamin C content were not determined. These data would indicate that while the antiscorbutic potency of canned sauerkraut may be variable, the product definitely contributes vitamin C to the diet.

The contribution of vitamin A by stored winter cabbage or canned sauerkraut is negligible.

KOHMAN, E. F., EDDY, W. H. AND GURIN, CELIA ZALL.

Vitamins in Canned Foods. XI. "A Canned Food Diet." Ind. Eng. Chem., 23, 1064, 1931.

White rats and guinea pigs were fed *ad libitum*, a diet composed of five canned foods selected to give a balanced diet. The combination of foods was changed every five days so as to include a wide variety of canned products in these tests.

Forty-nine commercially canned foods, purchased on the retail market, were fed in seventy-four combinations. No supplements of any kind were added to the diet; neither were the animals exposed to sunlight. In fifteen months, the experimental rats had reached the fifth generation. Rate of growth, reproduction, and lactation were normal in all respects in all generations, indicating that the canned food diet had adequately met all nutritive requirements.

A similar experiment, carried out with guinea pigs, resulted in normal growth, reproduction, and lactation through three generations in thirteen months. These experiments demonstrate that a diet composed exclusively of commercially canned foods meets the nutritional requirements of rats and guinea pigs during the complete life cycle. The significance of these results in human nutrition is that canned foods may be depended upon to supply in good degree the vitamins present in the raw foods from which they were prepared.

WHEELER, G. A.

The Pellagra-Preventive Value of Autoclaved Yeast, Canned Flake Haddock, and Canned Green Peas. U. S. Public Health Reports, 48, 67, 1933.

The pellagra-preventive value of commercially canned peas was investigated. Canned green peas were fed as a supplement to a basic diet which was known to produce pellagra in women. Daily allowances of 450 grams of this vegetable protected women from the disease during a year.

Toxic Absorption From the Bowel

● It is recognized that many symptoms in themselves far removed from the bowel, are the direct result of toxic absorption from the intestinal tract.

Soricin has been used with most gratifying results for detoxification of the intestinal content. Urticaria, angioneurotic edema, headache, vertigo, certain forms of eczema and other conditions when known to be caused by toxic absorption, have responded to the continued oral administration of Soricin over a reasonable period of time.

Clinical sample and additional literature to physicians on request.

Soricin

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Soricin and Bile Salts Tablets—Enteric coated tablets, each containing four and one-half grains of sodium ricinoleate, and one-half grain of bile salts.

ACTION: Detoxifies in vivo • Desensitizes • Inhibits putrefaction • Prevents toxic absorption.

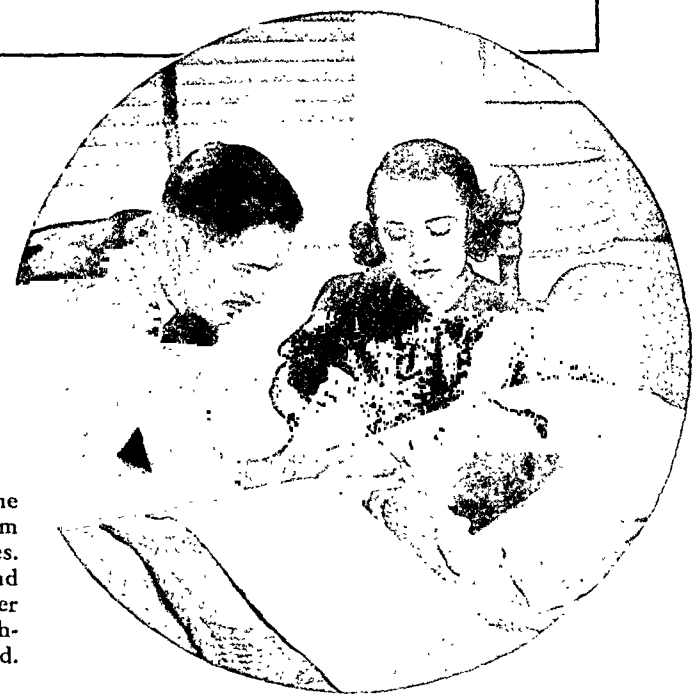
INDICATIONS: Bacterial Hypersensitivity of the intestinal tract • Intestinal toxemia • Intestinal allergy • Allergic diarrhea • Urticaria—angioneurotic edema • Colitis.

Literature and Sample on Request

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D. N. 5

Canned green peas are a valuable source of the pellagra-preventive factor.

WHEELER, G. A.

The Pellagra-Preventive Value of Canned Spinach, Canned Turnip Greens, Mature Onions and Canned Green Beans. U. S. Public Health Reports, 46, 2663, 1931.

Daily portions of 482 grams of commercially canned spinach was the source of the pellagra-preventive factor in the diet of 14 women. Thirteen of these women developed no symptoms of pellagra during a year, while one showed signs of the disease near the end of eleven months on the diet. These data demonstrate that canned spinach could well be included in the diet for the control of pellagra.

PARSONS, HELEN T. AND HORN, CAROLYN.

The Vitamin C Content of Commercially Canned Sauerkraut Produced Under Known Conditions. J. Agr. Res., 47, 627, 1933.

Four brands of sauerkraut produced under conditions as nearly identical as possible were examined biologically for vitamin C. One brand protected guinea pigs from scurvy when fed at the rate of 5 grams daily. The other brands were not such potent sources of vitamin C.

Cabbage was reported to be protective in daily doses of 2.5 to 5 grams, but, since this was not the same material from which the sauerkraut was prepared, direct comparisons can not be made.

Canned sauerkraut is considered a valuable source of vitamin C.

KOSITZA, LILLIAN.

A Comparative Study on the Use of Unsweetened Evaporated Milk and Bottled Cow's Milk in Infant Feeding. J. Pediatrics, 1, 426, 1932.

A group of 217 infants were studied by physicians at the Los Angeles City Welfare Conference. Of 217 normal feeding cases, 110 were given unsweetened evaporated milk and 107 were given bottled cow's milk. The formula of the unsweetened evaporated milk approximated that of bottled cow's milk. Supplements of vitamins A, C and D were given in the form of orange juice, tomato juice, and cod liver oil.

Observations were made upon 13 premature infants, 8 of which were given unsweetened evaporated milk and 5 bottled cow's milk.

Slightly larger gains in body weight made by infants given unsweetened evaporated milk, than by infants given bottled cow's milk. The increase in height of the infants on the two milks were about equal. Diarrhea was not as frequent in infants receiving unsweetened evaporated milk as in those receiving bottled cow's milk. Incidences of constipation were just about the same in the two groups. Infants fed unsweetened evaporated milk vomited a little more frequently. Aside from weight increases there were no appreciable differences in the performances of infants fed unsweetened evaporated milk and those fed bottled cow's milk.

From the standpoint of economy, availability, sterility, uniformity of composition, and ease of digestibility unsweetened evaporated milk has decided advantages over bottled cow's milk for infant feeding.

RICE, FRANK E.

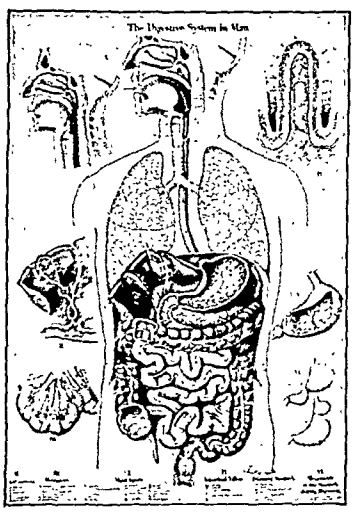
Protein, Minerals and Vitamins of Evaporated Milk. Am. J. Public Health, 24, 194, 1934.

The nutritive value and uses of evaporated milk are reviewed.

The heating of milk during evaporation brings about changes in its chemical, physical, and physiochemical properties. Due to these changes a finer curd is formed by the action of rennin or acid upon evaporated milk than upon raw milk. Protein, calcium, and phosphorus of evaporated milk, on a comparative basis with other forms of cow's milk are well utilized.

The vitamin A, D, or G content of milk is not affected by the processes of

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evaporating and canning. These processes reduce vitamin B content by about one-fifth, and vitamin C content to a considerable extent. The losses are not serious, however, because milk is not an important source of these vitamins and the diet should be supplemented with foods rich in them.

Evaporated milk diluted with an equal volume of water gives, at a very reasonable cost, a sweet milk for every use. The flavor of evaporated milk differs from that of the raw product; but, as with pasteurized milk, one becomes accustomed to the new flavor and develops a positive liking for it.

Its freedom from pathogenic organisms, ready digestibility, uniformity of composition, and economy recommend evaporated milk for infant feeding.

Report of Annual Meeting of Council on Pharmacy and Chemistry. J. Am. Med. Assn., 102, 1299, 1934,

The annual meeting of the Council on Pharmacy and Chemistry of the American Medical Association adopted the following units and standards for vitamins A and D.

Vitamin A

One unit U. S. P. X. (Revised 1934) = one unit International.

One unit U. S. P. X. (Revised 1934) = 0.714 unit U. S. P. X. (1925).

Vitamin D

One unit U. S. P. X. (Revised 1934) = one unit International.

One unit U. S. P. X. (Revised 1934) = 3.26 units A. D. M. A.

One unit U. S. P. X. (Revised 1934) = 0.37 unit Steenbock.

To be acceptable for inclusion in New and Non-official remedies, cod liver oil must contain not less than 850 units U. S. P. X. (Revised 1934) of vitamin A and 85 units U. S. P. X. (Revised 1934) of vitamin D per gram. The average recommended daily dose is, for infants, 12 ml. and for adults 24 ml.

To be acceptable, cod liver concentrates must contain at least 1,100 U. S. P. X. (Revised 1934) units of vitamin A, and 110 U. S. P. X. (Revised 1934) units of vitamin D per capsule or other dosage unit.

GOLDBERGER, JOSEPH AND WHEELER, G. A.

A Study of the Pellagra-Preventive Action of the Tomato, Carrot, and Rutabaga Turnip. U. S. Public Health Reports, 42, 1299, 1927.

Six ounces of juice from canned tomatoes were not effective for the prevention of pellagra; however, a daily dose of 40 ounces was effective for preventing pellagra in 18 women for over a year. The authors point out that their earlier idea about the lack of the pellagra-preventive in tomato juice was erroneous due to an unjust appraisal of the factor of quantity.



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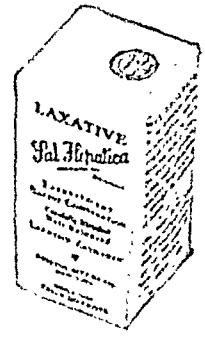
the mild saline aperient, offers essentially the same action as achieved by certain famous mineral waters. It helps to perform the two-fold function of waste elimination and alkaline conservation.

New experimental evidence indicates that Sal Hepatica stimulates an increased rate of bile flow from the gall bladder into the duodenum.

Sal Hepatica helps to combat tissue plasma acidity and to prevent mucous colitis resulting from retention of dry, irritating fecal masses. Support the disease-resisting factors of the body and eliminate waste material with Sal Hepatica. Send for samples and literature.

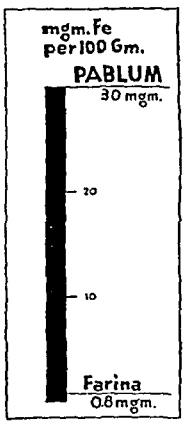
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FAR too often the bland diet prescribed for gastric ulcer, colitis, and similar gastro-intestinal disorders is a deficient diet. An analysis made by Troutt of ulcer diets used by 6 leading hospitals in different sections of the country showed them to be "well below the Sherman standard of 15 milligrams" in iron and low in the water-soluble vitamins.[1] "Vitamin B would appear to be represented at a maintenance level in most cases," writes Troutt, "but the possible relation of vitamin B to gastro-intestinal function and appetite should make one pause before accepting a low standard."



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Rich in Vitamin B

The high vitamin B content of Pablum assumes new importance in light of recent laboratory studies showing that avitaminosis B predisposes to certain gastro-intestinal disorders. Apropos of this, Cowgill says, "Gastric ulcer is another disorder which can conceivably be related to vitamin B deficiency. Insofar as the treatment of this condition usually involves a marked restriction of diet the occurrence of at least a moderate shortage of this vitamin is by no means unlikely."[2]

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a double boiler (studies *in vitro* by Ross and Burrill[3]). In addition to the above advantages, Pablum is the only base-forming cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum (Mead's Cereal thoroughly cooked) consists of wheatmeal, oatmeal, cornmeal, wheat embyro, alfalfa, yeast, beef bone, iron salt and sodium chloride. [1-3] Bibliography on request.

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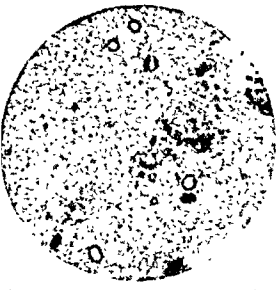
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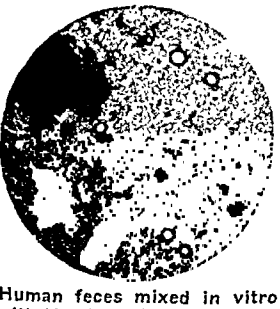
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SEBRELL, W. H.

Table Showing the Pellagra-Preventive Value of Various Foods. U. S. Pub. Health Rpts., 49, 754, 1934.

The pellagra-preventive value of various foods which have been thoroughly tested under controlled conditions in both dogs and humans are tabulated. Pellagra-preventive values are assigned on the basis of amounts fed; good indicating absence of pellagra in all subjects, fair signifying appreciable to considerable pellagra-preventive value with evidence of pellagra in one or more subjects, slight denoting the failure to prevent the disease but delaying onset and, none indicating the absence of pellagra-preventing value of practical importance.

Canned Food	Daily Amount (Grams)	Pellagra-Preventive Value
Beef, Corned	200	Good
Chicken	325	Good
Salmon	168	Good
Collards	482	Good
Kale	534	Good
Peas, Green	450	Good
Tomatoes, Juice from	1200	Good
Turnip Greens	482	Good
Haddock	340	Fair
Evaporated Milk...	15 c.c. per kilo of body weight	Fair
Cabbage, Green ...	482	Fair
Mustard Greens ...	533	Fair
Spinach	482	Fair
Beans, Green Stringless	550	Slight
Lettuce, Cos	516	Slight
Onions, Green	502	Slight

CALDWELL, G. W.

The Nutritive Value of Strained Vegetables in Infant Feeding. J. Pediatrics, 1, 749, 1932.

Pediatricians appreciate the value of foods rich in minerals and vitamins in the diets of young infants. In the past there has been some uncertainty as to the ability of young infants to digest, absorb, and tolerate supplements of vegetables.

In a series of experiments, strained vegetables were fed to 60 infants. The amounts fed daily were, 1 ounce up to 3 months, 2 ounces from 3 to 5 months, and 4½ ounces from 5 to 9 months. The strained vegetables were well tolerated by the majority of infants. The infants were practically free from digestive disturbances, in only 8 cases were the stools loose, and in these cases for only 2 to 4 days. Two infants vomited one feeding a day for one month.

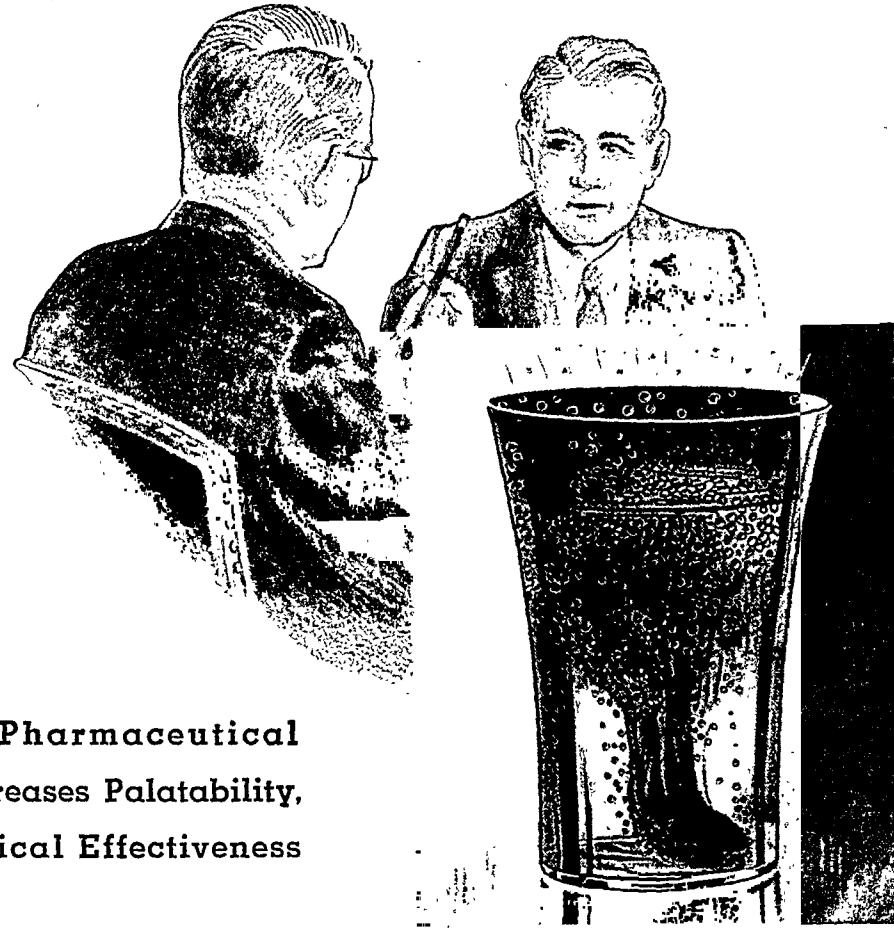
The results indicated that the feeding of strained vegetables contributed to the physical development and well being of the infants.

Properly prepared strained vegetables included in the diet aid in supplying adequate amounts of minerals and vitamins to assist in the promotion of optimum development of bone and teeth. Modern scientific methods enable manufacturers to prepare strained vegetables "in such a manner as to retain" a large portion of the essential minerals and vitamins.

KOHMAN, E. F.

Stabilizing Nutrients by Canning. Ind. Eng. Chem., 24, 650, 1932.

This paper is a general discussion of the contribution of the canning industry to present day problems arising from changing dietary demands. Fruits and vegetables are harvested at the proper stage of maturity when nutritive values are at a maximum and canned shortly after harvesting. Modern canning practices tend to preserve rather than diminish the inherent nutritive values which are rapidly lost upon storage in the raw state.



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TOLLE, C. D. AND NELSON, E. M.

Salmon Oil and Canned Salmon As Sources of Vitamins A and D. Ind. Eng. Chem., 23, 1066, 1931.

The vitamin A and D content of commercially canned salmon of five different species was determined by biological assay using albino rats. The oil was expressed from the canned product and fed in graded doses.

Vitamin A potency was not found to be high and it varied directly with the degree of pigmentation. Oil from two species of canned salmon had vitamin D potencies equal to that of medicinal cod liver oil, while a third species was found to be about one-half as potent.

From a consideration of the vitamin D values of salmon oil, the oil content of canned salmon and the quantity of canned salmon consumed annually in this country, it was concluded that this product supplies more vitamin D than the cod liver oil used for both human and animal feeding.

GOLDBERGER, JOSEPH AND WHEELER, G. A.

A Study of the Pellagra-Preventive Action of Canned Salmon. U. S. Public Health Reports, 44, 2769, 1929.

A moderately priced grade of commercially canned salmon (Alaska chum) was demonstrated to be a good source of the pellagra-preventive factor. Six ounces per day protected women from pellagra. Experiments with 18 women were continued for more than a year without the appearance of a single case of pellagra.

Canned salmon, a comparatively cheap, readily available preserved food, is a valuable addition to the diet in rural areas of the South in which pellagra is endemic in the spring and summer months.

WHEELER, G. A.

The Pellagra-Preventive Value of Canned Spinach, Canned Turnip Greens, Mature Onions, and Canned Green Beans. U. S. Public Health Reports, 46, 2663, 1931.

A pellagra-producing basic diet was supplemented with 482 grams daily of commercially canned turnip greens. Not a single case of pellagra developed in 15 women fed the above diet for more than a year.

The author concluded that turnip greens might well be included in any program designed to bring about permanent control of pellagra.

MILLER, CAREY D.

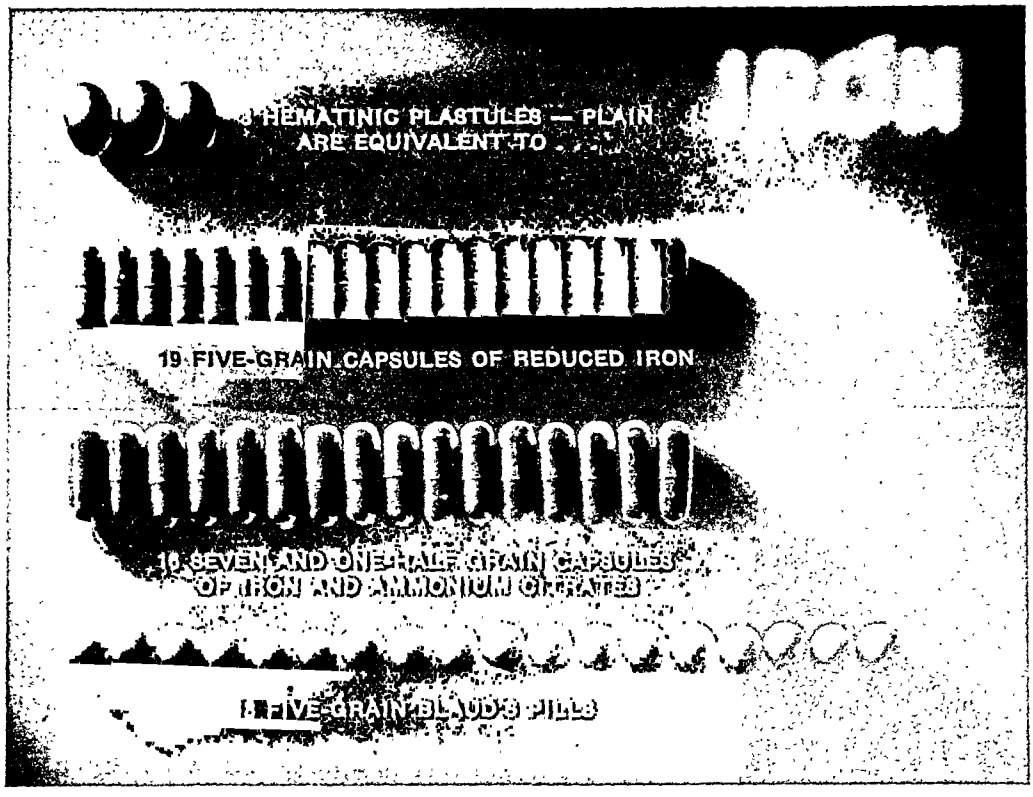
Vitamin C in Fresh and Canned Pineapple. J. Home Econ., 17, 377, 1925.

The low pH of pineapple helps to prevent any marked destruction of its original vitamin C content during the relatively light process which it receives when commercially canned. Since excellent growth rates were obtained from feeding 7 grams of canned pineapple and 5 ml. of the juice, it is considered a good source of vitamin C, being only slightly inferior to the fresh product.

MACLEOD, GRACE AND BOOHER, LELA.

The Antiscorbutic Content of Some Preserved Foods. J. Home Econ., 22, 588, 1930.

The vitamin C content of canned grapefruit is about equally distributed between the pulp and the juice. The loss of vitamin C during canning is estimated at between



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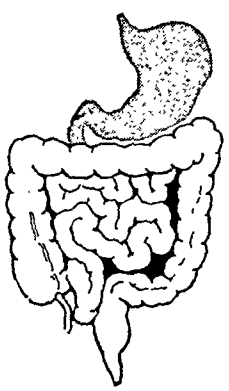


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*Am. J. Roentgen. 19:341, 1928 Am J. Med. Scien. 6:182, 1931.
**Arch.Int Med.38:647,1926.Am.J.Surg.7:455,1929.
***Ann. Int. Med. 6:1465. 1933. J. Lab. & Clin. Med. 19.567, 1934.

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10 and 15 per cent, placing the protective level somewhere between 2.2 and 2.8 grams. Rated in terms of units, canned grapefruit contains between 206 and 162 Sherman units per pound, which ranks it as one of the best sources of vitamin C.

GUERRANT, N. B., RASMUSSEN, RUSSEL A. AND DUTCHER, R. ADAMS.

The Value of the Chemical Titration Method in Determining the Vitamin C Potency of Certain Food Substances. J. Nutrition, 9, 667, 1935.

Canned sauerkraut juice was found by titration with 2,6-dichlorophenolindophenol to contain 0.082 mg. of ascorbic acid per milliliter. The calculated minimum protective dose for guinea pigs was 6.2 ml.

On the basis of these data canned sauerkraut juice may be considered a fair source of the antiscorbutic vitamin.

FELLERS, CARL R. AND ISHAM, PAUL D.

Vitamin C in Canned Citrus Products. J. Home Econ., 24, 826, 1932.

As a result of feeding tests on guinea pigs, it was found that approximately 1.2 grams of canned grapefruit slices afford protection from scurvy, which ranks it as one of the richest vitamin C foods.

One and one-half grams of canned grapefruit juice gave protection from scurvy, which also classes it as an excellent source of vitamin C.

The canned fruit used in this experiment had undergone from 6 to 9 months' storage.

WHEELER, G. A. AND HUNT, D. J.

The Pellagra-Preventive Value of Green Cabbage, Collards, Mustard Greens, and Kale. U. S. Public Health Rpts., 48, 754, 1933.

A pellagra producing basic diet was supplemented with 534 grams daily of commercially canned kale. A group of fourteen women was fed this diet for a year without the appearance of a single case of pellagra. Canned kale is a good source of the pellagra-preventive factor.

WHEELER, G. A. AND HUNT, D. J.

The Pellagra-Preventive Value of Green Cabbage, Collards, Mustard Greens, and Kale. U. S. Public Health Rpts., 48, 754, 1933.

A pellagra producing basic diet was supplemented with 482 grams of commercially canned collards daily. Thirteen women were fed this diet for a year without a single case of pellagra appearing.

Commercially canned collards could be used for the control of pellagra in the rural sections of the South.

WHEELER, G. A. AND HUNT, D. J.

The Pellagra-Preventive Value of Green Cabbage, Collards, Mustard Greens, and Kale. U. S. Public Health Rpts., 48, 754, 1933.

A pellagra producing basic diet was supplemented with a daily serving of 482 grams, including the can liquor, of commercially canned green cabbage. One case of pellagra developed in 16 women kept on the diet for a year. 482 grams was the border line dose of this vegetable.

Canned green cabbage is a valuable food for supplementing the diet in the rural areas of the South to control pellagra.

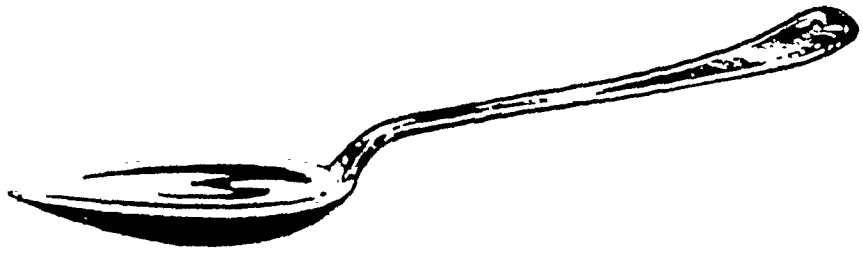
WHEELER, G. A. AND HUNT, D. J.

The Pellagra-Preventive Value of Green Cabbage, Collards, Mustard Greens, and Kale. U. S. Public Health Rpts., 48, 754, 1933.

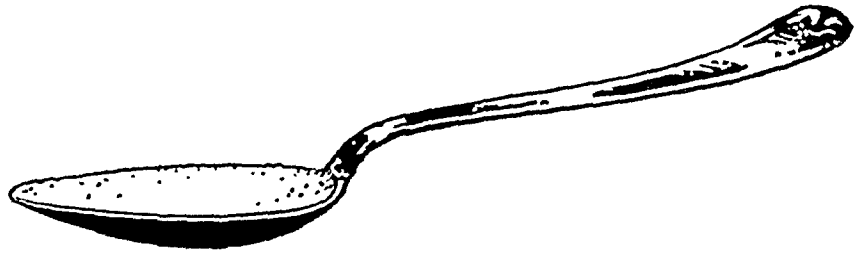
A pellagra producing basic diet was supplemented with 533 grams, including the can liquor, of commercially canned mustard greens. One case of pellagra developed in 14 women kept on this diet for a year.

Canned mustard greens are a fair source of the pellagra-preventive factor and could well be included in the diet for the control of pellagra.

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Synopsis of

Digestive Diseases

By JOHN L. KANTOR, Ph.D., M.D.,
Associate in Medicine, Columbia University.
260 pages, 40 illustrations. Price, $3.50.

This book presents simply, clearly and concisely, the essential facts concerning the diseases of digestion. An effort has been made to preserve the proper balance between *stress and subordination, inclusion and omission*; and to emphasize throughout the ways in which gastro-enterology fits into the larger field of internal medicine. To this end the opening chapter on classification has been designed for early orientation, clinical syndromes common to many diseases have been elaborated as fully as possible, and a final section has been devoted to digestive symptoms in extradigestive diseases.

In the preparation of this book the writer has drawn on his clinical records for much of his basic statistics, as well as on his practical experience in *teaching gastro-enterology* to both undergraduate and graduate students. The current literature, in periodicals and in special monographs, has been carefully, and it is hoped critically, utilized.

The illustrations, most of them original, and all of them drawn especially for this book, include several synoptic charts devised for the diagramatic presentation of the more important diseases. The special diet forms are derived in practically all instances from the Montefiore Hospital Manual of Diets.

Synopsis of

Ano-Rectal Diseases

By LOUIS J. HIRSCHMAN, M.D., F.A.C.S.,
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288 pages, 174 illustrations. Price, $3.50. 6 color plates.

This work goes into detail especially in the technic of methods of diagnosis and details of treatment which can be administered without the use of general anesthesia. Many methods of office treatment are described and clearly illustrated. Care has been taken to present methods of treatment which do not require complicated or expensive electrical or other apparatus. It does not attempt to treat of the major diseases of the rectum or of the colon but is designedly limited to the treatment of the commoner diseases of the anus, anal canal and the rectum. The diagnosis, however, of *major conditions such as carcinoma*, are included of necessity in order to avoid pitfalls for the unwary.

This synopsis has all the salient material of the Fourth Edition of Hirschman's "Handbook on Diseases of the Anus and Rectum" condensed and brought up to date and in addition many methods of diagnosis and treatment which should assist the general practitioner of medicine in acquiring a better knowledge of those diseases of the anus and rectum which are amenable to treatment outside of the purview of the specialists.

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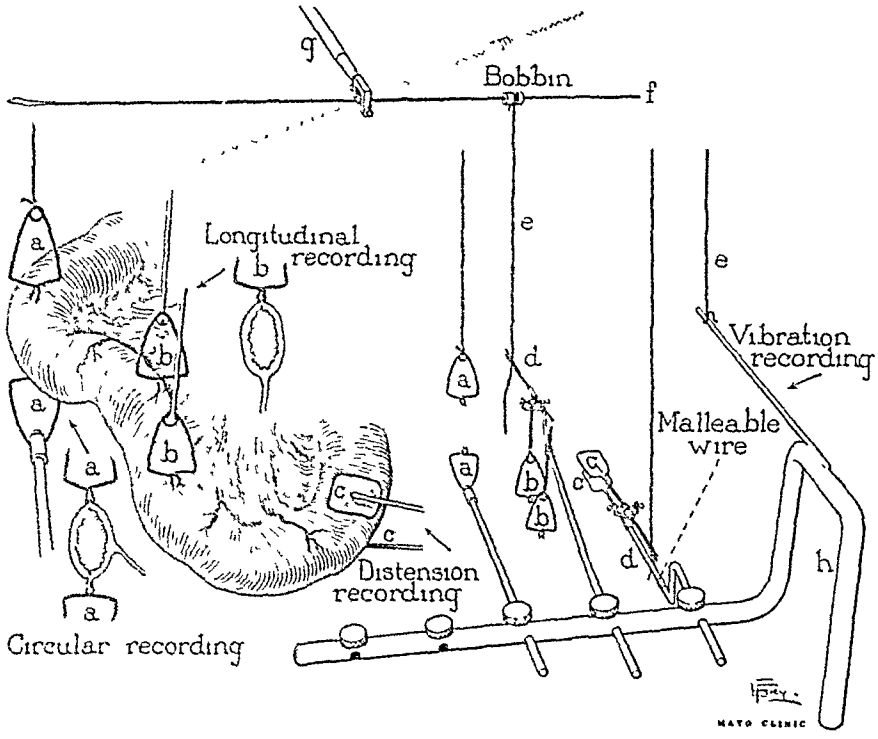


Fig. 1

a, recorder for circular muscle; *b*, recorder for longitudinal muscle; *c*, distention recorder; *d*, small wire crotches for pinching and holding thread; *e*, *f*, and *g*, writing lever; *h*, bar which is clamped to side of tank.

recorder one has to make a little rent in the bloodless, transparent part of the mesentery, but this does not seem to have any injurious effect. Occasionally one may have to tie the bowel in place with the help of a fine thread put through the mesentery.

The tracings made with the distention recorders usually showed oscillations due to the rhythmic contractions of the bowel. It seemed at times, also, as if the distention recorder were serving somewhat as a plethysmograph to record small changes in the volume or thickness of the wall of the bowel. All in all, I think this new recorder is the best available for the recording of rush waves in the intestine of the rabbit.

Records made simultaneously with the help of the three types of enterographs attached to one short segment of bowel. Records were made during the passage of rushes through a short segment of bowel, usually several centimeters long, to which were attached the three types of recorders. In this way I could see not only how the records differed, but also, by placing distention recorders at the oral and caudal ends of the segment, with a circular and a longitudinal recorder in between, I could tell when fluid entered and left the segment and could distinguish between relaxation and distention.

When a rush passed, all four records usually looked much the same, all the levers having risen and fallen in unison. If the circular and longitudinal recorders had shown distention by a fall in the record, as I originally expected them to do, the tracings obtained with them should have been mirror images of those obtained with the distention recorders. Actually, it was only occasionally that the circular and longitudinal apparatus recorded distention as a drop in the level of the record.

Although puzzles remain, the tracings made with the distention recorders now show happenings that correspond well with the impressions gained by the observer while he watches rushes passing through nicotinized bowel or bowel injured by anoxemia. They show occasional distention which is not followed by active contraction, but only by a slow tonic restoration of the original diameter of the bowel. They help also in distinguishing between a normal rush and an imperfect one, something which the old recorders commonly failed to do.

Unfortunately for the student of peristalsis who would like to differentiate abnormal and normal rushes, even fast rushes in apparently normal animals do not always run down the bowel evenly as one might expect them to do. Occasionally the records will show that a particular segment was suddenly distended with fluid or gas and thus stimulated to contract at a time when the crest of the oncoming wave was still 50 cm. orad. At other times it will be seen that a segment contracted ahead of time in spite of the fact that no fluid had yet entered it. Not infrequently, also, the person who watches a big wave will get the impression that it consists of a series of disconnected short rushes, and yet the records of distention will show that each time, as a contraction died out, some of the moving column of fluid seeped on and apparently gave rise to a rush further caudad. In other cases the recorders show that a definite shallow ripple passed from one active segment to another, invisible to the unaided eye.

With the distention recorder a good quick rush in a normal bowel commonly produces in the tracing a sharp peak. When the neuromuscular mechanism of the bowel has been injured by anoxemia or nicotine, there may still be a sudden distention, with a sharp rise of the point of the lever, but then it drops slowly during a period of a minute or more. During this

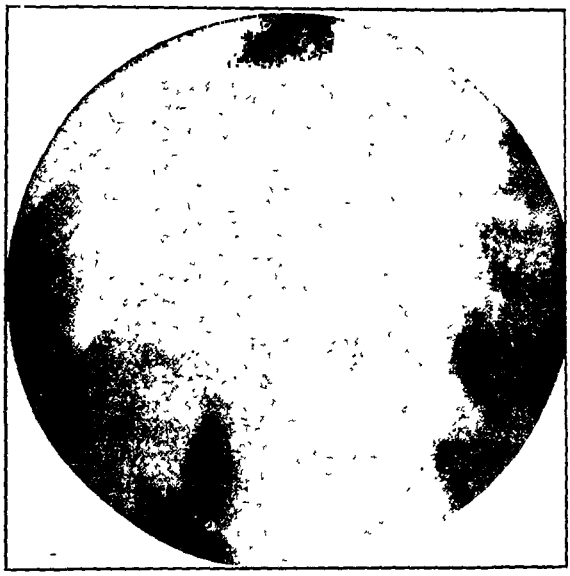


Fig. 1. Showing typical pancreatic stones.

40 to 45 units of insulin a day were required to control glycosuria.

On the first physical examination there were no significant findings other than moderate emaciation. Marked glycosuria, with a fasting value for blood sugar of 163 mg. per 100 c.c., was noted. Roentgenologic examinations of the gastro-intestinal tract and gall bladder were negative; those of the small bowel did not reveal any demonstrable abnormality. A test of liver function with bromsulphalein showed no retention of dye, the rate of hippuric acid conjugation was normal, the serum bilirubin was normal in amount and reaction, and there was no reduction in serum protein (7.24 gm. per cent). The serum lipase, which is usually elevated in acute pancreatitis, was within normal limits. Complete absence of pancreatic secretion was demonstrated by studies on the duodenal content. Roentgenograms of the upper part of the abdomen disclosed numerous small calcified areas which seemed to be distributed throughout the body of the pancreas (Fig. 1). There was some question as to the benefits which might be derived from operation, but it was nevertheless felt that exploration was justified in the hope that the pancreatic duct could be freed of stones. At operation a mass of adhesions was found in the right upper portion of the abdomen; the gall bladder was slightly distended, the common duct was about twice the normal size, and the liver was apparently normal. The pancreas was much firmer than normal and was enlarged to about three times the normal size. Since it seemed that the stones could not be removed from the pancreatic ducts without grave risk, only cholecystostomy and choledochostomy were performed in the hope of relieving the pancreatic infection presumed to be associated with the condition.

Following operation the patient got along well for about three months when marked diarrhea appeared, as it had at various times in the past. He had as many as twelve stools in twenty-four hours; they were of an offensive odor, and were bulky and fatty. Since this steatorrhea was obviously due to deficiency of external pancreatic secretion and it did not respond to symptomatic measures, pancreatic juice obtained from dogs according to the method of Bargen, Bollman and Kepler was administered by duodenal tube and in a dried form. The details of this study are reported elsewhere; suffice it to say here that there was prompt and definite improvement in the patient's condition, the number of stools decreasing to two in twenty-four hours. He was allowed to return home and got along fairly well until the summer of 1936 when he again experienced attacks of abdominal pain similar to those described earlier. Following such episodes of pain, glycosuria and diarrhea increased, and following the last attack, in September, 1936, slight jaundice and marked ascites and edema made their appearance.

On physical examination at the clinic at this time enlargement of the liver was noted, its edge being palpable 8 cm. below the costal margin. The spleen was definitely enlarged, and a few distended veins were visible over the abdominal wall. The stools contained only a moderate amount of fat and the diabetes was about of the same severity as before, requiring 40 units of insulin daily for control. The fasting value for blood sugar was 200 mg. per 100 c.c. On two examinations the duodenal juices were found to contain no pancreatic ferments whatever. Blood smears revealed macrocytosis typical of disease of the liver. The bromsulphalein test of liver function revealed retention of dye grade 3; the hippuric acid test showed some reduction in liver function (2.26 gm. calculated as benzoic acid). The value for blood cholesterol was 192 mg. and for cholesterol esters 136 mg. per 100 c.c.; serum proteins were 7.3 gm. and serum bilirubin 2.9 mg. per 100 c.c., the van den Bergh reaction being direct.

In discussing the physiologic aspects of this case with Dr. Bollman, who had prepared the pancreatic juice used in the treatment of the patient's steatorrhea, the possibility of fatty change in the liver due to the primary pancreatic lesion was first considered. While attempting to obtain a supply of lipocaic for treatment, it was decided to attempt to control the ascites and edema by increasing the intake of carbohydrate, by giving ammonium nitrate in full doses and by intravenous injections of salyrgan. On this regimen distention of the abdomen decreased rapidly and the peripheral edema disappeared. Through the courtesy of Dr. Dragstedt, sufficient lipocaic for twelve days' use was supplied. During that period the liver definitely decreased in size, and dye retention which had previously been graded 3 was reduced to grade 1. Later protamine insulin was substituted for ordinary insulin, about 80 units being given on alternate days. At the time of dismissal the diet consisted of 250 gm. of carbohydrate, 60 gm. of protein, and 122 gm. of fat (2,340 calories). The patient was considerably improved generally; there was no ascites or edema and the fatty diarrhea was under satisfactory control.

On March 1, 1937, the patient wrote that he was feeling remarkably well, that there had been no return of the ascites or edema, and that the diarrhea had not recurred. The administration of lipocaic will be continued for an indefinite period.

In this case there is good evidence to show that the primary pancreatic lesion was of long duration and that whatever lesion developed in the liver was of much more recent date and of rapid development. Hepatic functional tests and careful inspection of the liver at operation, early in 1935, did not reveal any significant changes; the hepatic and splenic enlargement, the ascites and edema, and other evidences of hepatic involvement appear to have developed acutely a year later. It is possible, but by no means certain, that the immoderate use of alcohol hastened the process. The prompt improvement under treatment, the decrease in the size of the liver and reduction in dye retention when lipocaic was given, and the marked and rapid general improvement in the patient's condition argue for a diffuse fatty change rather than for the presence of the ordinary forms of portal cirrhosis.

In Case 2, the available information is less conclusive, but the clinical picture is very suggestive of a more or less identical change in the liver. Here again

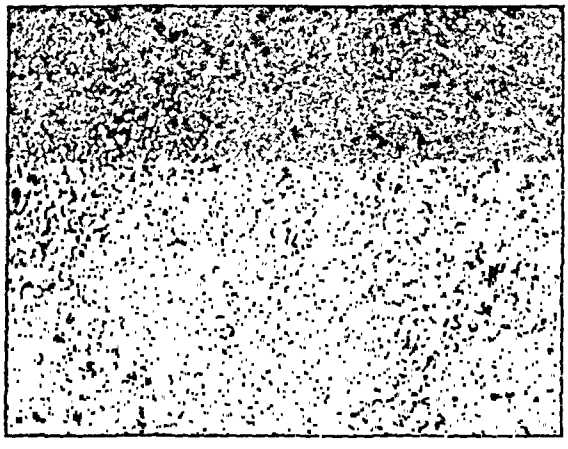


Fig. 2. Fatty infiltration of the liver of a patient with extreme pancreatic atrophy (x100).

there is little to suggest the possibility of a permanent type of structural hepatic damage, although the pancreatic lesion was undoubtedly of long duration:

Case 2. The patient, a physician, aged forty years, came to the clinic in January, 1936, complaining of intermittent jaundice and abdominal cramps. There was a history of alcoholism, and many of his digestive complaints were more or less intimately associated with drinking bouts. On reviewing the history, the patient described attacks of upper abdominal pain which were projected to the left and were accompanied by nausea, chills, vomiting and fever. Jaundice and diarrhea had accompanied or followed these attacks. During the two years preceding registration at the clinic, the patient had lost 50 pounds (22.7 kg.) and had become extremely nervous and weak. Shortly before coming to the clinic ascites and edema had developed.

On physical examination the patient was found to be weak, pale, and slightly jaundiced. The abdomen was distended with fluid and a number of large superficial veins were observed over the anterior abdominal wall. The edge of the liver was felt about 4 cm. below the costal margin; the spleen was also moderately enlarged. Because of the patient's poor condition, he was hospitalized and a tentative diagnosis of portal cirrhosis and ascites was made. Urinalysis was essentially negative; the value for hemoglobin was 13.3 per 100 c.c., and erythrocytes numbered 4,200,000 and leukocytes 7,100 per cubic millimeter of blood. The differential count was essentially normal, but morphologic examination of the blood smears revealed a "toxic" blood picture with definite macrocytosis. The plasma coagulation index and number of platelets were normal, 1.3 and 170,000, respectively. Blood urea, blood sugar, and plasma chlorides were, respectively, 16, 95, and 608 mg. per 100 c.c. The serum protein was 5.63 gm. per 100 c.c. and the albumin-globulin ratio 1.08:1. The blood cholesterol and cholesterol esters were, respectively, 89 and 60 mg., and the blood calcium was 8.8, phosphorus 3.2 and phosphatase 7.2 mg. per 100 c.c. Two tests for serum lipase gave results of 0.7 and 0.35 c.c., respectively, as measured in cubic centimeters of tenth normal sodium hydroxide. The Takata-Ara test was strongly positive. A liver function test with bromsulphalein showed dye retention, grade 1. The serum bilirubin reading was 1.4 mg. and gave a direct reaction. The benzoic acid excretion was 3.22 gm. in four hours. Roentgenologic examinations of the thorax, stomach, small intestine, colon and terminal portion of ileum were negative. A cholecystogram showed a nonfunctioning gall bladder and multiple pancreatic calculi. Stool tests showed oil and fat in excess and contained bile in good quantities, the total fat in one specimen measuring 16.3 per cent. Duodenal drainage revealed bile in normal quantities, but there was no amylase or trypsin present.

A diagnosis was made of chronic pancreatitis with lithiasis, pancreatic insufficiency with absence of external pancreatic ferments, and secondary hepatic change, presumably due to fatty degeneration. Treatment with a high carbohydrate diet, glucose intravenously, and small doses of salyrgan, produced a remarkable diuresis and relief from ascites and edema. Some general clinical improvement was noted while the patient remained in the hospital and subsequent correspondence indicated that he had done fairly well except for attacks of abdominal pain.

In comparing the course of this patient with that in Case 1 it seems quite likely that this patient's principal complaints were due to primary pancreatic lithiasis with secondary fatty changes in the liver, the latter factor being, no doubt, affected by the use of alcohol. The laboratory evidence of rather moderate parenchymatous hepatic damage and the ease with which ascites and edema cleared under treatment suggests again a fatty type of liver rather than one which was the site of nodular cirrhosis. In a third case, in which the findings will not be presented in detail, pancreatic lithiasis, steatorrhea, and diabetes mellitus have been demonstrated; the evidence of hepatic damage rests upon a single positive bromsulphalein test, a moderately elevated icterus index, and a slightly enlarged liver; it will be interesting to see if more definite signs of hepatic insufficiency will ensue at a later date.

COMMENT

In the cases just described, hepatic insufficiency of various degrees appeared as a probable sequel of pancreatic lithiasis and pancreatic insufficiency. On reviewing the literature it was found that in a few cases of pancreatic stone or atrophy the liver had been described as affected in various ways. Most authors describing cases of chronic pancreatic atrophy or lithiasis, however, do not mention hepatic changes, the reasons being that complete pancreatic insufficiency due to stone is of relatively uncommon occurrence and that extensive destruction of pancreatic tissue is probably required to produce any fatty deposits in the liver. Fiessinger and Olivier (1933), however, comment on the association of hepatic disease in cases of pancreatic lithiasis and reported a case with proved cirrhosis. Vallery-Radot and his colleagues described another case in which pancreatic stones were associated with cirrhosis and primary malignancy of the liver. Choy and Oh have described the case of a young woman whose pancreas was affected by lithiasis; at necropsy the liver weighed 1,560 gm. and was very fatty. Paviot and his associates (1935) reported an almost identical case, the liver weighing 2,050 gm. and showing extreme fatty degeneration. In a recent case reported by Thompson, McQuarrie and Bell there was hypoproteinemia, ascites, and edema; at necropsy a very fatty and somewhat atrophic liver was found, but there was no description of any lesion in the pancreas which might explain it. Binger and Keith's case of ascites and edema of indeterminate origin, with complete atrophy of the pancreas and a fatty liver, was strikingly similar to the last two mentioned. Because of its intimate bearing on the subject and the completeness of their study, we have obtained their permission to present it in some detail:

The patient, a man aged sixty-two years, came to the clinic in February, 1934, complaining of edema and ascites which had been present for about five months. There was an antecedent history of fatty diarrhea extending over a period of about five years; numerous and varied diets and medications had failed to relieve the condition.

On physical examination the patient was found to be pale and weak. There was a small amount of fluid at both lung bases and the abdomen was distended with fluid, but neither the spleen nor liver could be made out. Peripheral and general edema was also noted. Urinalyses were negative, with albumin appearing only in traces; renal functional studies revealed mild renal insufficiency. The serum protein was 3.6 gm. per 100 c.c. and the albumin-globulin ratio was 1:1.6. The blood cholesterol was low (75 mg. per 100 c.c.). A liver function test with bromsulphalein showed dye retention, grade 3, and a later one retention of grade 2. Blood studies were interesting, revealing definite marked anemia; the value for hemoglobin was 11.5 gm. per 100 c.c.; erythrocytes numbered 3,750,000, and leukocytes 9,600 per cubic millimeter. Examination of the smears was not diagnostic, but active erythrocyte regeneration was noted. Gastric analysis showed an absence of free hydrochloric acid. Successive stool tests showed an excess of fat or oil but were otherwise negative. The patient was given a high protein diet, together with raw liver, Adex tablets and calcium lactate. Potassium nitrate and salyrgan produced satisfactory diuresis, with a loss of 37 pounds (16.8 kg.) of edema fluid.

No definite diagnosis was established, and the condition was classified as one of the indeterminate edemas associated with hypoproteinemia. The question of pancreatic disease was raised, but there was no proof to support such a diagnosis other than the fatty stools. It was agreed that the patient had a hepatic lesion of some type, but its nature was uncertain. He returned to his home where he gradually failed and died on April 7, 1934.

A complete postmortem examination revealed multiple cysts of the pancreas, with extreme atrophy of the pancreatic tissue, bilateral hydrothorax, hydropericardium and ascites. Microscopic section of the pancreas revealed only a few ducts, moderately dilated, practically no acinar tissue, and no islands of Langerhans. Between the ducts there was a large amount of dense connective tissue. No evidence of fat necrosis and no signs of any specific inflammatory phenomenon could be demonstrated. There was sufficient anatomic basis to conclude that there was practically total pancreatic insufficiency, certainly of the acinar tissue, and possibly also of the islands.

The liver showed extensive fatty changes in the cells and terminal congestion of the sinuses, but there was no other fundamental pathologic change except for extreme fatty infiltration (Fig. 2). There was no increase in connective tissue or suggestion of cirrhosis. No renal pathologic change was observed grossly or microscopically.

There was some question as to whether or not the fatty change in the liver was sufficient to account for the ascites, edema, and hypoproteinemia, but in view of the cases previously described and the work which has been reported on pancreatectomized animals, it seems reasonable to suppose that fatty degeneration of the liver secondary to pancreatic atrophy existed.

A search of the records of the Department of Pathology at the clinic reveals nine cases of pancreatic lithiasis, the essential details of which have been described by J. G. Mayo. In three cases there was some degree of fatty change; the remainder showed no striking change in the liver except in one case with hemochromatosis where cirrhosis was a feature. In only one of the remaining cases was destruction of pancreatic tissue complete; one must therefore assume in the others that sufficient pancreatic tissue was present to maintain normal fat metabolism. Quite probably a further search of clinical and postmortem material will reveal other cases in which pancreatic disease is followed by parenchymatous hepatic lesions of a fatty type.

SUMMARY AND CONCLUSIONS

Experimental and clinical evidence is cited which seems to demonstrate: (1) the occurrence of fatty degeneration of the liver when there is extensive destruction of the pancreas, (2) that the absence of the hormonal substance, lipocaic, may be the inciting factor for these changes in the liver, and (3) that there may be some therapeutic use for this preparation in certain clinical cases of pancreatic disease. If this is not available, the feeding of raw pancreas and diets high in lecithin is suggested. The possible relation of fatty change to the later development of cirrhosis invites speculation.

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Hydrogen Peroxide as a Depressant of Gastric Acidity*

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A GREAT amount of work has been done in search of methods for decreasing the acidity of the gastric contents. One of the substances which has been used for this purpose is hydrogen peroxide. Petri (1) in 1908 reported that large quantities of a dilute solution (300 c.c. of a 0.5% solution) introduced into an empty stomach markedly lowered the acidity of the gastric contents and recommended its use in the treatment of hyperacidity. Since then a number of clinicians (2, 3, 4, 5, 6 and 7) have reported that dilute hydrogen peroxide is a means of reducing the secretion of gastric acid and of increasing the secretion of mucus. All agreed that acid secretion was reduced, but not all recommended its therapeutic use. The degree of inhibition of acid reported varied. Hurst (8) in 1931 reported the use of hydrogen peroxide for relieving the achlorhydria or hypochlorhydria seen in chronic gastritis. He used solutions varying from 0.013% to 0.095% as a gastric lavage. It is to be noted that Hurst used hydrogen peroxide in much more dilute solutions than did the others. He supposed that it was an effective mechanical means of dislodging the excessive mucus which was present in chronic gastritis. He suggested that excessive mucus prevented acid secretion by blocking the mouths of the acid-secreting glands.

For some time one of us (A.J.A.) has been interested in studying experimentally the effects on gastric secretion of various agents when applied to the gastric mucosa of animals. Our review of the literature indicated that the effect of hydrogen peroxide on gastric secretion should be studied under controlled laboratory conditions. This we have done; in addition we have extended our studies to include a few human subjects.

METHODS

Five Pavlov pouch dogs and three dogs with intact stomachs were used. All were in good health at the time the experiments were initiated. Five clinic patients were studied; the clinical diagnosis was duodenal ulcer in three, and gastric ulcer in one; one had a normal stomach insofar as could be determined by physical findings and laboratory tests, but he complained of dyspepsia and epigastric distress.

The secretion of the pouch dogs was collected by the orthodox method. In the dogs with intact stomachs the gastric contents were aspirated by means of a number 32 French colon tube which was passed each time a sample was to be withdrawn. We first tried using a retained Rehfuss tube; it worked well during the control tests, but after hydrogen peroxide had been administered there was so much mucus on subsequent aspirations that the small tube invariably became occluded. In the human subjects a Rehfuss tube was used.

Two methods of stimulating the gastric secretion were used. Histamine was used in all three groups of subjects; in each case 1.0 mgm. of ergamine acid phosphate was injected subcutaneously. In addition, on the dogs with pouches, tests were made in which the stimulus was a test meal.

In the dogs with pouches when histamine was used as the stimulus, a control test started with the injection of the histamine, the gastric samples being collected several times during a period of 90 minutes. At the end of 90 minutes another milligram of histamine was injected and the collection of juice continued. In the dogs with intact stomachs and the human subjects, only one test period of 90 minutes was employed. In the case of the dogs with pouches when a meal was used as a stimulus, the secretion was collected for a period of eight hours after feeding.

In the case of each subject a number of control tests were made to establish the normal response of the individual to the stimulus being used.

RESULTS

The complete data are too bulky to be presented. Therefore we shall give a representative protocol of one of the experiments and will then summarize the results obtained in the remainder.

The effect of a single application of 3.0% hydrogen peroxide on the histamine response: Dog No. 1 had a Pavlov pouch. On injecting 1.0 mgm. of histamine the pouch secreted an average of 14.0 c.c. of gastric juice containing 53 mgm. of free HCl and 63 mgm. of total acid in 90 minutes. After the necessary control tests, the pouch was washed with 100 c.c. of 3.0% hydrogen peroxide (see Table I). Beginning 15 minutes later the secretion of the pouch was collected for two 30 minute periods. During this time the secretion was mucoid in nature, amounted to 18.2 c.c., and contained no free acid, but had a slight amount of total acid. Then 1.0 mgm. of histamine was injected subcutaneously. In 90 minutes 23.2 c.c. of secretion were collected containing only 6.00 mgm. of free HCl and 21.60 mgm. of total acid. Then the injection of histamine and collection of secretion were repeated with the results shown in Table I. The results of all these particular experiments on Dog No. 1 are included in Table II. The results show clearly that washing the pouch with 3.0% hydrogen peroxide markedly depressed the secretory response to histamine. The juice was rich in mucoid secretion.

In the five dogs in which this experiment was performed, the free HCl secretion was reduced on the average 65.8% after the first injection of histamine and 56.5% after the second. The volume of mucoid secretion obtained varied widely, but was increased in all.

Following a single treatment of the pouch with

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hydrogen peroxide, the dogs were injected daily with histamine to determine the time at which the secretory response returned to normal. The time of recovery varied widely. One dog had not returned to normal in 29 days. One returned to normal in 5 days, one in 9 days, one in 10 days, and one in 12 days. One secreted hypernormally at 12 days, one at 15 days, and another at 18 days.

The effect of repeated applications of 3.0% hydrogen peroxide on the histamine response: In two of the dogs whose response to histamine had returned to normal in from five to nine days after a single application of hydrogen peroxide, 3.0% hydrogen peroxide was applied to the pouch twice daily, morning and evening, for 15 days. The response to histamine was determined on the third, fifth, eighth, eleventh, and fifteenth days. The secretion of free and total acid was reduced markedly in both dogs. In one dog the free acid was reduced by 96% (almost abolished), the total acid being reduced 83%. In the other the free acid was reduced 77% and the total acid 46%. The volume of secretion, chiefly mucoid, was reduced 23% in one and increased 48% in the other. From the first dog, on some days, a clear rather dilute mucoid secretion devoid of free acid (pH 4.2) was obtained.

The effect of a single application of various concentrations of hydrogen peroxide on the histamine response was studied in the three other dogs with pouches. It was found that a 0.5% solution was effective in reducing the secretion of acid, the average varying from 12% to 66% in the total acid and from 32% to 83% in free acid in the different dogs. The results, as might be anticipated, showed that the stronger the concentration the greater the reduction in acid secretion. Concentrations of 0.5, 1.0, 1.5, 2.0, and 3.0% were employed.

The results with a meal as the stimulus: After the pouches had returned to normal and suitable response to the test meal had been obtained, the hydrogen peroxide was applied and the meal fed. The secretion of the pouch after the meal was collected for eight hours.

The data are shown in Table III. The results are exceedingly variable, much more so than the results obtained with histamine as a stimulus. This should be expected because the response to the stimulus of a meal is normally more variable than the response to histamine. The variation may be about 25% from day to day in the same dog. Further, after the first hour or two following the application of the peroxide and feeding, acid secretion starts to increase. The amount of secretion varies in the same and different dogs. It must be recalled that the histamine response occurs only during a period of from one to one and one-half hours. It is to be noted that a 3% solution was required to produce a definite reduction of the free acid in two of the three animals in series 2; and in series 1, dog No. 2 showed little decrease even to 3.0%.

In one dog (No. 8) a 2% solution was effective. Dog No. 11 manifested a definite increase in acid secretion after the application of each of the concentrations of peroxide except the 3% solution. This is the animal that showed the most marked hypernormal response to histamine during the recovery of the pouch from the effect of 3% peroxide.

TABLE I

The effect of a single application of 3.0% hydrogen peroxide on the histamine response

Time	Vol. in c.c.	C.U. Free Acid	mgm. Free Acid	C.U. Total Acid	mgm. Total Acid	Remarks
9:25						Pouch washed with 100 c.c. of 3.0% hydrogen peroxide. Started collecting.
9:40						
10:10	12.0	-0-	-0-	½	0.12	
10:40	6.2	-0-	-0-	4	0.62	
	18.2				0.74	
10:40						Injected 1.0 mgm. histamine.
10:55	2.8	-0-	-0-	8	0.84	
11:15	7.5	8	2.25	25	6.75	
11:25	3.0	18	2.10	68	7.50	
11:40	3.3	13	1.65	35	4.20	
11:55	2.6	-0-	-0-	18	1.82	
12:10	4.0	-0-	-0-	4	0.40	
	23.2		6.00		21.60	
12:10						Injected 1.0 mgm. histamine.
12:25	5.8	-0-	-0-	8	1.74	
12:40	5.7	15	2.85	40	8.55	
12:55	3.9	25	3.51	53	7.41	
1:10	2.6	15	1.30	43	4.16	
1:25	2.2	8	0.66	25	1.98	
1:40	2.8	-0-	-0-	15	1.40	
	23.0		8.32		25.24	

Dogs with normal stomachs. Three dogs with intact stomachs were treated with 100 c.c. of 3% hydrogen peroxide after several control responses to histamine had been obtained. The peroxide solution was withdrawn after three minutes. The secretion of free acid was reduced from 95% to 100%, and the total acid was reduced from 81% to 90%. The secretion of mucus was so copious that a colon tube had to be used to aspirate the gastric contents. The dogs were nauseated and retched after the aspiration of the peroxide. One of the dogs on being treated again on the following day showed a large amount of blood in the gastric contents.

This depression of secretion was anticipated. The greater viscidity of the secretion probably was due to stimulation of the mucosa of the pyloric antrum in addition to that of the fundus. Nausea and vomiting did not occur in the dogs with Pavlov pouches for several reasons. The area to which the peroxide was applied was smaller. The nauseating effects of the stomach tube were absent. In the animals with whole stomachs some of the hydrogen peroxide undoubtedly passed into the duodenum. Three per cent peroxide obviously was too irritating for the stomach of one of the animals.

HUMAN SUBJECTS

Because 3.0% hydrogen peroxide was found to be markedly irritating to humans, 1.0% and 2.0% solutions usually were employed. A 3.0% solution was used in the "normal" individual in a few tests. Histamine was used as a stimulus. The entire content of the stomach was removed every ten minutes for 90 minutes after the injection of histamine. From three to five control responses to histamine were obtained prior to the commencement of treatments with hydrogen peroxide. The stomach was lavaged with from 100 to 300 c.c. of the peroxide which was withdrawn after three to five minutes. This procedure was repeated two or three times a week, until four to twenty treatments had been given.

In one patient with duodenal ulcer in which only 1.0% peroxide was used, the acid secretion after five treatments was increased by about 35% in spite of the

TABLE II

	1st Injection of Histamine					2nd Injection of Histamine				
		Free acid		Total acid			Free acid		Total acid	
	Vol.	MxCU	mgm.	MxCU	mgm.	Vol.	MxCU	mgm.	MxCU	mgm.
Controls										
1	15.4	130	63.47	148	69.90	8.7	177	37.10	193	40.71
2	10.0	128	37.74	150	42.80	8.2	183	32.59	143	36.13
3	12.9	128	45.43	145	58.80	10.1	130	39.05	138	43.90
4	17.7	133	64.17	143	79.98	15.7	138	68.92	145	75.69
Averages	14.0	130	52.95	146	62.87	10.7	144	41.44	155	49.11
Using 3% hydrogen peroxide										
1	15.5	20	4.55	38	12.16					
2	16.9	38	15.09	53	23.54					
3	19.2	53	22.61	65	31.51	18.2	88	42.32	103	52.27
4	23.2	18	6.00	68	21.60	23.0	25	8.32	53	25.24
5	13.2	20	4.62	53	16.85	15.5	55	19.54	80	34.84
6	16.5	25	7.31	50	16.76	15.6	40	16.13	65	30.31
7	13.0	63	22.12	88	32.76	21.0	88	47.25	118	68.42
8	9.5	15	3.42	38	9.95	3.5	0	00.00	26	2.34
9	15.1	38	11.94	58	21.01	13.7	33	5.80	48	15.06
10	8.5	25	5.54	48	12.00	4.1	25	3.55	48	7.03
11	15.8	35	10.33	55	11.85	16.1	43	15.52	65	27.20
12	8.8	38	4.88	55	9.53	9.7	78	24.87	95	16.96
Averages	14.6	32	9.87	56	18.32	14.0	48	18.33	70	27.97
Per cent of change from control averages	Inc.	Dec.	Dec.	Dec.	Dec.	Inc.	Dec.	Dec.	Dec.	Dec.
	4.3	75.4	81.4	61.6	70.6	30.8	66.6	58.7	54.8	43.0

Vol. — volume in c.c.
MxCU — maximum clinical units
mgm. — milligrams of free or total acid in terms of HCl
Inc. — increase
Dec. — decrease

formation of considerable mucus. Because the lavage caused discomfort and because the symptoms were augmented, the treatment was discontinued. In a second duodenal ulcer patient similarly treated, the free acid secreted was decreased by 45% and the total

TABLE III

	Vol.	Free acid		Total acid	
		MxCU	mgm.	MxCU	mgm.
1st series 3%					
Dog No. 1	30.9	85.2	96.7	77.6	90.2
Dog No. 2	5.5	10.8	11.5	3.6	6.4
2nd series ½%					
Dog No. 1	1.8	9.9	10.1	2.2	9.7
Dog No. 8	34.4	62.3	74.2	21.6	60.8
Dog No. 11	19.2	23.2*	49.7*	21.6*	31.9*
1%					
Dog No. 1	21.7	27.2	45.4	19.4	38.6
Dog No. 8	45.8	61.6	77.4	20.7	65.6
Dog No. 11	10.4*	33.9*	181.7*	12.2*	95.8*
1½%					
Dog No. 1	54.1*	43.8	27.7	36.6	10.5
Dog No. 8	4.6	32.6	36.8	11.7	26.0
2%					
Dog No. 1	10.5	24.0	27.2	23.1	11.9
Dog No. 8	21.2	57.9	68.3	25.2	63.8
Dog No. 11	13.6	21.4*	32.5*	14.8*	25.3*
3%					
Dog No. 1	10.7*	52.0	58.8	44.0	49.2
Dog No. 11	32.9*	67.8	63.8	52.7	46.1

The figure shows the average per cent of change from the control response; those marked with an asterisk represent percentage increases, the others decreases.

acid by 18%; this patient secreted much mucus. Because the symptoms were not decreased, the treatment was discontinued. The stomach of the third patient with duodenal ulcer was lavaged eight times with 1.0% and 2.0% solution of peroxide. Five tests were performed during a three week period. Discomfort from the lavage occasionally was reported. The two per cent solution of peroxide decreased the free acid values by about 90% and the total acid values by about 30%. The symptoms of this patient disappeared with this regime without other medication or dietary changes. In the patient with a gastric ulcer, 1.0% solution of peroxide increased the secretion of both acid and mucus; 2.0% caused a decrease of about 50% in the acid values. The treatment was discontinued because the patient's symptoms were not relieved after nine treatments during a period of four weeks, and because there so frequently was considerable blood in the gastric contents following hydrogen peroxide. In the individual with a "normal" stomach, concentrations of peroxide varying from 1.0% to 3.0% were used. Twenty treatments were given and nine tests were done during this time. More patients were not used because of the discomfort and bleeding experienced by those we did treat in this way.

The results of the tests confirmed the observations on the dogs, that 3.0% solution of peroxide reduced acid values in response to histamine to a greater extent than the 1.0% solution. In the patient with gastric ulcer and in one of three patients with duodenal ulcer a 1.0% solution of hydrogen peroxide increased the acid values of the stomach contents after histamine. In the other two patients with duodenal ulcer either 1.0% or 2.0% solution of hydrogen peroxide reduced the acid values after histamine. In the individual with a "normal" stomach 1.0% to 3.0% solution of hydrogen peroxide lowered the acid values in response to histamine, the stronger solution being the more effective.

DISCUSSION OF RESULTS

The preceding results indicate that in general the lavaging of the stomach with hydrogen peroxide solution (½-3%) produced a decrease in the acid of the gastric contents when either a meal or subcutaneous injection of histamine was used to stimulate acid secretion. This decrease was observed in the per cent of acid in the gastric contents and in the total milligrams of acid, both free and total, in each case. The stronger the solution of hydrogen peroxide used the greater was the decrease of acid response. This decrease varied widely in different subjects, and also, from time to time, in the same subject. However, one of the dogs and two of the five human subjects consistently showed increases in acid secretion rather than decreases. The mucous secretion always was augmented.

At times there was a complete absence of free acid (but no instances of complete absence of total acid) in response to histamine stimulus. This was observed four times in dog No. 1, once in dog No. 2, twice in dog No. 8, twice in dog No. 6, twice in dog No. 9, and twice in dog No. 12. However, it was the exception rather than the rule. This type of secretion was observed by Ivy (9) and Dawson (10) in the gastritis produced in Pavlov pouch dogs by X-rays.

While no chemical analyses for content of mucus were made, it was obvious that generally an increase in mucoid or mucus secretion paralleled a decrease in acidity. This observation certainly was true in those tests in which no free acid was found. In several instances when there was no free acid, determinations of the chloride in the secretion were made; and it was found that the chloride content was no higher than that which is normal for mucus or mucoid secretion.

Other investigators have reported using 300 c.c. of a 0.5% solution for gastric lavage of peptic ulcer patients. Petri, Poly, Hall, Kelling, and Dienst were enthusiastic in regard to the use of hydrogen peroxide in the treatment of peptic ulcer because the secretion of acid is reduced and that of mucus is increased. Hall stated, however, that it did not seem to benefit cases with active ulcer. Winternitz found that it decreased acidity for only short intervals, and discarded its use. Nielson also observed a depression of free acid with a return to normal values or nearly normal values in 24 hours. Hurst used dilute solutions (0.013-0.095%) in chronic gastritis, observing an increase in acid secretion.

Our results show that to obtain a significant reduc-

tion in acid secretion in response to histamine or a meal, stronger concentrations of peroxide (one and two per cent) must be employed. Even then stimulation, as observed by Hurst with very weak solutions, may occasionally occur. A three per cent solution is too irritating. When the weaker solutions are used the return of the secretory response to normal is relatively rapid. In the case of a "susceptible" stomach, however, a 0.5% solution applied every other day will reduce acid secretion significantly. However, we suspect that it might cause active ulcers to bleed; for the gastric ulcer patient showed bleeding with one and two per cent solutions, and one of the dogs with "normal" stomach showed marked bleeding after 3%. Although it would be desirable to have some simple and innocuous method for reducing the secretion of acid by the stomach, we do not feel that the use of hydrogen peroxide can be recommended without considerable reservation.

CONCLUSIONS

1. Hydrogen peroxide in solutions varying from one-half to three per cent when used as a gastric lavage may depress the acidity of the gastric contents. This may be true even when using histamine as the gastric secretory stimulus. However, in an occasional dog and human subject a one or two per cent solution may induce a stimulating effect. The individual susceptibility varies widely, a three per cent solution being required to depress significantly acid secretion to histamine in some individuals.

2. The stronger the solution of peroxide used, the greater is its effect in depressing the acidity.

3. Hydrogen peroxide influences the volume of gastric secretion in response to a stimulus. The volume of secretion may be either increased or decreased. The volume changes do not correlate with the changes in acidity.

4. Hydrogen peroxide stimulates the secretion of mucus by the stomach.

5. The effects of hydrogen peroxide on gastric secretion are most marked immediately after lavage. Recovery occurs in from 24 hours to 15 days, depending on the individual susceptibility and the concentration of peroxide used.

6. Hydrogen peroxide is not a satisfactory means of depressing gastric acidity in patients. It may be active in inducing hemorrhage from an ulcer. When used in the most effective concentrations it causes too much discomfort, and its effect in concentrations which do not cause discomfort cannot be predicted.

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A Contribution to the Etiology of Gall Stones*

III. A study of the hydrogen-ion concentration of gall bladder bile and its effect upon gall stones

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IT has been definitely established that the hydrogen-ion concentration of gall bladder bile varies in different animals. In the herbivorous animals the bile is normally alkaline (1), while in the carnivorous animals the bile is more likely to be acid (2). On the other hand, in the human subject an omnivorous species, the hydrogen-ion concentration is close to the neutral point (3).

The fact has been well established that human gall stones will readily dissolve in dog's bile, the reaction of which is acid, the pH. averaging about 6.1 (1). We have observed that human gall stones do not dissolve in the guinea pig's gall bladder bile, which is normally definitely alkaline (4).

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In the present investigation, an attempt has been made to render alkaline, the normally acidic dog's gall bladder bile. This was accomplished by the following method. The gall bladder was exposed and brought out to the surface and sutured to the peritoneum and skin. After the wound healed, a fistulous gall bladder was produced by opening the exposed vesicle and allowing it to drain freely. The purpose of this procedure was to prevent concentration of the bile in the gall bladder and yet maintain bile in the vesicle. In order to accomplish the latter objective the fistulous opening was allowed to heal almost completely, but still to permit a small amount of drainage. Inasmuch as these fistulas tended to heal completely in most instances, it was necessary to keep them open by frequent probing.

TABLE I

The hydrogen-ion concentration of bile in the fistulous dog

Dog	Control bile pH.	Hydrogen-ion concentration readings						
4		8.67	7.98	8.84				
6		7.9	7.5	6.85				
7	5.89	8.32	7.71	8.78	6.06	5.86	8.72	
8		6.48	8.60	8.56	6.32	8.37	8.20	8.40
9	6.01	6.08	7.48	7.50	7.12	7.34	7.02	8.42
		8.81	8.31	8.40	8.40	8.40	7.50	7.28
		8.56	8.46	8.56	8.68	8.47	8.60	8.80
		8.74	6.40	7.96				
11	6.25	8.55	7.55	8.40	8.81			
12		8.75	6.75	8.77	7.70	8.42	8.56	
17	6.52	8.71	8.70	8.55	6.66	7.98	6.05	8.87
		8.11	8.81	8.82	9.35	8.76		
20		8.45	8.80	8.65				
21		8.32	8.52					

TABLE II

The pH of the bile and its effect upon cholesterol gall stones in gall bladder fistulas

Dog	Weight of stone placed in gall bladder	Weight of stone after removal	Number of days	Loss or gain in grams	pH.
6	2.3505	1.7126	79	—0.6379	7.90
					7.50
					6.85
9	0.5803	0.4885	27	—0.0918	8.42
					8.81
					8.31
					8.40
					8.40
17	0.3145	0.1553	18	—0.1592	6.66
					7.98
					6.05
20	0.3075	0.830	61	+0.5225	8.45
					8.80
					8.65
8	3.521	5.841	49	+2.320	8.37
					8.20
					8.40

It is interesting to point out that these fistulous gall bladders presented also histopathological abnormalties. The mucosae were preserved, but distinct thickening of the gall bladder wall with lymphocytic infiltration was noted, indicating evidence of a chronic inflammatory process. Table I presents the hydrogen-ion concentrations of gall bladder bile made at varying intervals from the fistulous gall bladders. It is interesting to note from these experiments that the gall bladder bile is persistently alkaline if the fistulous opening is patent and the drainage is free, but since the opening has a tendency to close the bile tends to return to acid. The color of the fistulous bile is light yellow having the appearance of liver bile, while the normal gall bladder bile of the dog is dark green.

The premise upon which the present investigation is based is that human gall stones do not tend to dissolve in alkaline bile. This has been clearly demonstrated in the guinea pig and reported in a previous communication (4).

In nine dogs with satisfactory fistulae made in the manner already described, in which the acid bile of the dog becomes alkaline, (see Table I) further studies were made as to its effect upon stones. In order to demonstrate the effect upon the weight of the stone, it was noted that loss of weight diminishes as the proportional degree of hydrogen-ion concentration of the gall bladder bile increases, i.e. the greater the alkalinity of the bile the less effect it has on the dissolution of stones. A human gall stone was inserted in each of five dogs' gall bladders through the fistulous opening. Table II presents the hydrogen-ion concentrations of the gall bladder bile. The table clearly demonstrates the effect of alkaline bile upon human gall stones in relation to the pH. values of the bile. It would seem

that the alkalinity of bile seems to favor the formation of stones as deduced from the fact that alkaline bile does not dissolve stones and often favors an increase in its weight. This is quite in contrast to the effect of normal dog's bile upon human gall stones which has been shown to lose on the average of about 70 per cent or more of its original weight (1).

CONCLUSIONS

Our experimental investigations indicate that the change in the hydrogen-ion concentration of gall bladder bile is an important factor in the etiology of gall stones.

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Peristalic Rush Studied with New Apparatus*

By

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AS everyone knows, food and its residues are moved down the bowel at intervals with the help of peristalitic rushes. In the rabbit, these rushes commonly start in the duodenum about the time that a large gastric wave reaches the pylorus. They can be started by causing the animal to swallow fluids, and after going some distance they are likely to fade out or to be stopped, perhaps by an increase in the tonus and activity of the bowel out ahead. A rush in the upper part of the bowel is commonly associated with rushes farther caudad in the ileum or colon, rushes that seem to be started by a stimulus which shoots rapidly from one end of the digestive tract to the other. It is this stimulus which produces the changes in tonus and activity already referred to as appearing in segments far out ahead of the traveling disturbance (1, 2).

Mahoney and I showed that there are two important parts to a rush; one, a wave of contraction traveling in the wall of the gut, and the other, a column of fluid being pushed ahead through the lumen. This column of fluid can be compared to a long train of cars with an engine behind. If one ties a piece of tape gently about the bowel, the column of fluid is stopped and the wave in the wall goes on to pick up a new column beyond the obstruction, but if one cuts the bowel across and connects the ends with a piece of glass tubing, the wave in the wall is stopped while the column goes on to pick up a new wave in the muscle beyond the tube.

METHODS OF STARTING PERISTALTIC RUSHES

Several years ago I began to start peristaltic rushes in rabbits with the help of a measured and uniform stimulus. To obtain this, I squirted into the proximal part of the duodenum 10 c.c. of Locke's solution, under a pressure of 100 mm. of mercury. With the animal anesthetized and pithed in the way described elsewhere (3), a cut was made in the side of the bowel, and the lower end of a specially made burette (designed by Dr. Joseph Berkson) was tied in. This burette, about 30 cm. long, has two side-tubes and a cock at each end. The lower side-tube is connected with a flask containing Locke's solution, and the upper, with a flask containing air. The first flask and its contained fluid are warmed by immersion in the large tank of Locke's solution in which the animal is lying.

In order to fill the burette, one opens the cock in the lower side-tube and the one at the upper end and pumps air into the upper part of the fluid-containing flask with the help of a rubber bulb. As the salt solution is forced up into the burette, it raises a light bakelite piston which fits loosely in the lumen. The two open cocks are then closed, the cock on the upper side-tube is opened, and air is pumped in above the piston until a manometer in the circuit shows a pressure of 100 mm. of mercury. When the experimenter wishes to produce a rush he opens the cock at the bottom of the burette and the fluid squirts into the bowel. The expanding air above is kept from entering the bowel by the piston, which comes down against a ring of small knobs on the inner surface of the lower end of the burette, and is stopped there.

The moment of stimulation is recorded on the drum by means of a writing lever connected by a thread to the evacuating cock. The burette is held in place by a stand which must not touch the tank holding the animal. In order to avoid artefacts in the records care must be taken not to jar the bowel, the animal, or the tank just before a rush is started.

Still further to avoid doubt on this point, I fastened each of the six recorders used in an experiment to one end of a short segment of soldering wire which was then set in a hole in a bar clamped to the side of the tank, as in Figure 1, *h*. The use of such easily bent soldering wire is a great help because with it the experimenter can place the various recorders exactly where he wants them without having recourse to a troublesome forest of rods and clamps. I then added the lever and recording apparatus marked *e* in Figure 1, so that the slightest jarring of the clamp *h* would be magnified and recorded on the drum.

Solutions used in the burette. A number of fluids were used in the burette, such as plain water, soapy water, and slightly acid or alkaline solutions, but nothing seemed to be much more effective than Locke's solution. Slightly acid and slightly alkaline solutions

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were somewhat more provocative of rushes, but I returned to the use of Locke's solution because it has the great advantage of being least injurious to the delicate mucosa of the bowel.

The importance of the column of fluid. That the presence of fluid in the lumen of the bowel helps in the production of rush waves was shown by the fact that when the segment of duodenum into which fluid was squirted was closed off from the bowel below by a band of tape applied just tightly enough to occlude the lumen, it was not so easy to start waves on their way down through the jejunum. Even less effective than squirts of fluid were electric and mechanical stimuli applied to the wall of the duodenum.

APPARATUS USED FOR RECORDING PERISTALSIS

The balloons commonly used by many workers constitute foreign bodies which are undesirable (1) because they obstruct the lumen of the bowel and thus interfere with the passage of rushes; (2) because the muscle keeps contracting powerfully in an effort to move the foreign body onward; (3) because, at least in the rabbit, the gut tends to gather on the tube leading to the recording apparatus, and (4) because there is considerable trauma where the cut is made for the insertion of the tube. Because of all these objections I long ago gave up the use of balloons as recording devices. I soon saw that if I were ever to succeed in recording the rush waves of the bowel, I must attach the apparatus to the peritoneal surface so as to leave the lumen clear. Accordingly, I fastened recorders of several types to the peritoneal coat (Alvarez and Mahoney). Although good records could thus be obtained, I was never quite satisfied because there was always some blocking of the passing waves due to the irritation and trauma produced by the little pinching clips.

"Circular" recording unsatisfactory. My dissatisfaction with existent methods of recording became acute some six years ago when my assistants and I found that although, to the unaided eye, it appeared that peristaltic rushes skipped a segment of bowel poisoned by nicotine, graphic records made by attaching threads and light levers to several points along the affected segment showed what looked like the passage of a normal rush.

Eventually it occurred to me that since we were recording movements of a loop of circular muscle gripped between two little wire clips, as in Figure 1, *a*, the pull of the lever on the empty bowel would tend to flatten it until its cross section would resemble that of a rubber band, and the distance between the two clips would represent approximately half of the circumference. When, however, the bowel had become filled and its cross section had become a circle, the distance between the clips would represent the diameter. Since the diameter is less than half of the corresponding circumference, one should expect, with this method of recording, to see the writing point of the lever rise when the gut filled, and calculation showed that the difference between the half of the circumference and the diameter, when magnified by the lever, should amount to about 3 cm. Actually, when loops of dead bowel were distended with water, this was the amplitude of the movement observed, and at last I saw why so many of the records obtained had been confusing or unintelligible.

A "longitudinal" recorder. In order to avoid the defect in the "circular" recording device, I designed the simple piece of apparatus pictured in Figure 1, *b*, and with it recorded movements of the longitudinal muscle. A small weight was usually placed on the short arm of the little lever so as to balance the moving part and make the apparatus more sensitive. Contractions of the muscle between the clips should depress the end of the first lever and produce a rise on the record.

As soon as I placed the new longitudinal enterographs on nicotinized segments of gut I was again puzzled to find, in most of the tracings, records of what looked like normal rushes, although, as I watched the bowel, I still failed to see any wave of contraction in the poisoned segment. Occasionally, distention of the bowel would produce the expected drop in the level of the record, but commonly it did not, and I was driven to the conclusion that the longitudinal enterographs must often respond to distention of the segment with a confusing upward movement of the writing point. This conclusion was supported by the results of an experiment in which a segment of dead bowel was distended with fluid. What happened, apparently, was that a segment of bowel, when filled, tended to form an arc because the length of the mesenteric side is fixed by connective tissue, and the antimesenteric side alone can stretch.

The distention recorder. When the longitudinal enterograph was found to be unsatisfactory, I next designed the "distention recorder," shown in Figure 1, *c* and *d*. It consists of two little bronze "hands" which hold the bowel between them. One is fixed and the other is movable. The pivot for the movable arm is taken from a heart lever made by the Harvard Apparatus Company. An upward movement of the upper "hand" or spatula, due to distention of the bowel, causes an upward movement of the writing tip of the lever. The illustration fails to show a little sliding weight usually placed on the arm near the attachment of the thread almost to balance the weight of the spatula. The little bobbin on the lever can be rotated to shorten the thread and to make necessary adjustments in the height of the record on the drum. A little bit of wire soldered to the movable arm of the recorder makes a tight crotch which serves to pinch and hold the lower end of the thread. These two very convenient, simple, and time-saving accessories were added by Dr. Joseph Berkson.

With the two little slightly curved spatulas holding the bowel gently between them, it seemed as if the passage of the smallest amount of fluid would have to be recorded as a rise in the level of the tracing, and actually, the excellence of the records obtained with this apparatus exceeded all my expectations. This recorder seemed to be more sensitive than either of the other two because when the three were placed side by side on a short segment of gut, the record of distention commonly revealed weak "long distance effects" and little surges of fluid up and down the bowel, which had not had any effect on the other two recorders.

This greater sensitiveness may perhaps be due to the fact that with this light instrument the bowel is not irritated or traumatized, and there is almost no obstruction to hold back or stop the progress of waves. In order to place the bowel between the blades of the

An Office Procedure for the Rapid Estimation of Pepsin and Its Clinical Significance*

By

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ESTIMATIONS of pepsin have not been commonly made in routine gastric analysis because of the lack of a convenient "office" method for its quantitative determination. The procedure utilizing Mett's tubes was the standard for a long time but it has now been given up by most workers (1). Several of the more recently described methods have gained favorable comment and are probably used to some extent. However, for most of them the preparation of the substrate is time-consuming if not difficult (2, 3). For others, very careful technique must be employed as well as apparatus not usually found in the practitioner's office (4, 5). There is obviously a need for a simple and rapid, yet reasonably accurate procedure. The method to be described meets these requirements; it employs no elaborate apparatus; and uses as a substrate milk treated with a buffer, which is easily prepared and which keeps indefinitely. With this method we have made several clinical observations, which are of considerable interest and importance.

METHOD FOR DETERMINATION OF PEPSIN IN GASTRIC JUICE

The method is based on the fact that the milk-clotting action of human gastric juice at a pH of 5.0 is really an early stage of proteolytic digestion of casein by pepsin and that there is no rennin in human gastric juice (6). In other words, milk-clotting under these conditions is a function of the pepsin molecule (7). Therefore the concentration of pepsin may be estimated by measuring the milk-clotting power of the gastric juice, using the strongly buffered milk as a substrate. The same principle is the basis of other methods (5, 8). Fresh cow's milk (raw or pasteurized) is employed and, when mixed with an equal volume of the buffer, becomes a substrate which is easily reproducible, and which rules out pH changes occurring in the milk and in the gastric juice.

Preparation of Standard Milk Substrate. The buffer is prepared by dissolving 42 g. of NaOH in about 500 c.c. of distilled water, adding 115 c.c. of 80% acetic acid and diluting to 1000 c.c. with distilled water. Fresh cow's milk is diluted with an equal volume of this buffer, 200 c.c. of the buffered milk is usually ample for one determination. This buffered milk, having a pH of 5.0, was first suggested by Ege and Menck-Thygesen (8).

Preparation of Gastric Juice. Three cubic centimeters of gastric juice (or less, if this amount is not available) are diluted with an equal volume of distilled water, mixed well and filtered.‡ One cubic centimeter of the filtrate is now diluted to 12.5 c.c., making a total dilution of 1:25, and one cubic centimeter is diluted to 25 c.c., a dilution of 1:50. A preliminary test is made to determine the approximate clotting power in the following manner: 10 c.c. of buffered milk are placed in each of two test-tubes and 1 c.c. of the 1:25 gastric juice is added to one and 1 c.c. of the 1:50 to the other. Both are placed in a water bath at 20° C.§ and watched for the first appearance of a clot. If the 1:25 does not clot the milk in 10 minutes, undiluted gastric juice is indicated for the final test. If the 1:25 clots in 5-10 minutes, this dilution is indicated, whereas if the 1:50 clots in 5-10 minutes this more diluted gastric juice is to be used. Ten tubes are now set up, each containing 10 c.c. of buffered milk, and placed in a water bath at 20° C. To these tubes are now added 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 c.c. of the indicated diluted gastric juice, respectively. The contents of each of the tubes are quickly mixed and kept for 10 minutes at 20° C. The smallest amount which produces a clot is observed, and the number of cubic centimeters of milk clotted by one c.c. of gastric juice is calculated. Since we define a unit as the amount of pepsin which will clot one c.c. of buffered milk in 10 minutes at 20° C., the figure determined equals the number of units in the specimen.

Calculation:

Formula. Units of pepsin per c.c. original gastric juice $= \frac{1}{\text{volume diluted gastric juice}} \times$ degree of dilution x 10.

For example: If 0.6 c.c. 1:50 gastric juice is the smallest amount which will clot 10 c.c. buffered milk in 10 minutes, then 1/0.6 x 50 x 10 = 1.67 x 500 = 835 units per c.c. original gastric juice.

Test Meals: We have employed two types of test meals, i.e., plain and with meat. The former consists of eight arrow root biscuits and 600 c.c. water. The meat meal contains in addition 15 g. chopped lean beef, which had been boiled for one hour in 500 c.c. of water.

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Submitted March 17, 1937.

‡In achylia gastrica cases, however, the original gastric juice is diluted with an equal volume of 0.1 N HCl instead of water before filtration to activate any inactive pepsinogen which may be present. Here no further dilution may be necessary and several cubic centimeters of the acidified gastric juice may have to be used. Even then no clot may occur. If there is a suspicion that regurgitation has taken place, the determination is likely to be inaccurate since trypsin reacts similarly to pepsin. All of our patients had been intubated several times previous to these tests and consequently regurgitation was quite unlikely. If the presence of trypsin can not be avoided, one of the more elaborate procedures for the estimation of pepsin must be used.

§A cup or tumbler of tap water will ordinarily answer the purpose, since tap water is usually about this temperature.

time the intestinal contents are moving slowly out of the segment. But even when the bowel is apparently normal and rushes are good, they do not all produce good narrow "steeples."

The peak made by the passage of a rush wave through the segment of bowel lying within the two spatulas of the distention recorder is commonly sharper at the top and narrower at the base than that made by the other two recorders on the circular and longitudinal muscles, which indicates that the muscle remains contracted and active for some time after the loop empties. This tendency of the bowel to remain contracted for several seconds after a rush wave has passed was plainly apparent in the motion pictures of peristalsis made and studied by Zimmermann and me, and its value in preventing regurgitation of intestinal contents orad was pointed out by us.

As the observer watches a rush he often gains the impression that the wave was not sequent but that several rushes took place along the bowel about the same time, and the records may show that this actually was the case. As I said before, when the stimulus is thrown into the duodenum, an impulse of some kind shoots down the length of the intestine. Responding promptly to this fast traveling stimulus, some segments of bowel begin to contract three or four seconds before the arrival of the main wave, much as a runner in a relay race will get under way before his team-mate arrives. For convenience I speak of the phenomenon as "anticipation."

The "long distance" stimuli also cause little surges to take place along the bowel. These are revealed as little rises in the records of distention, due to the entrance of a little fluid into a segment. These rises may appear from five to ten seconds before the main column comes rushing in.

Fortunately, now, by putting distention recorders at the oral and caudal ends of a short segment, with circular and longitudinal recorders in between, one can tell when fluid enters and leaves the segment and one can study the reaction of the muscle of the bowel to the presence of such fluid. Only rarely did I see what might be interpreted as signs of relaxation or inhibition in the longitudinal or circular records at times when I could be sure that the fall in the level of the record was not due to distention caused by the entrance of fluid into the segment.

THE SEVERAL PEAKS ON A WAVE

A peristaltic rush, no matter how powerful, does not empty the small bowel from one end to the other; it seems to push material ahead for a short distance only to drop it and pick up more further on. As a result, the main crest of the wave is often followed by one or more "scavenging waves" which serve to move fluid out of segments that have been left somewhat distended. Curiously, the interval of time between any two peaks on a wave, as it travels from one end of the bowel to the other, is often kept remarkably constant. Occasionally, the record will show that one of the several peaks was made by a little surge that ran orad for some distance while the main wave was going on caudad.

To show how complicated a rush can be, I will describe an actual record made as a wave passed a set of four recorders. First, about twenty-five seconds before the main column of fluid arrived, there were signs of inhibition, with a lessening of the amplitude of the rhythmic contractions; second, one rhythmic contraction was entirely blocked; third, there was distention of the segment due to the passage of a small amount of fluid; fourth, there was contraction of the muscle; fifth, there was marked distention produced by the passage of the main column of fluid, and sixth, there came the final contraction that emptied the segment.

WATER WAVES

Occasionally, when a long segment of poorly functioning bowel failed to empty itself of the fluid squirted in, I could see in the distention records, made simultaneously at several points along the length of the segment, what I call a "water wave"; that is, a small peak like that of an artefact, appearing everywhere at the same time, and due apparently to a disturbance transmitted through the fluid. Such water waves might easily lead to false interpretations if the experimenter were to interpret them as signs of rapid nerve conduction. They can be avoided either by not allowing the bowel to fill with fluids, or by placing a bit of tape around the bowel, just tight enough to obstruct the lumen.

SUMMARY

A simple apparatus is described for squirting, with measured force, a measured amount of fluid into the duodenum. In normal rabbits, each such stimulus usually produced a peristaltic rush. It did not seem to make much difference what type of fluid was injected.

Two enterographs, attached to the peritoneal coat and designed to record separately the movements of the circular and the longitudinal muscles, produced tracings which, while helpful, were not satisfactory for reasons that have been given in this paper. Accordingly, a new enterograph was devised which records principally distention of the bowel and the passage of fluid through the lumen. It has the great advantage of not traumatizing, irritating, or obstructing the bowel.

Records obtained with this apparatus helped to differentiate normal and atypical or pseudo-rushes. The normal rush produced in the record sharp peaks which were due to a rapid distention of the bowel, followed by a prompt contraction of the muscle and emptying of the segment. Abnormal rushes tended to produce a somewhat flat-topped elevation in the record, due to slow and deficient emptying of the bowel.

What looks like a rush may be a series of contractions or short waves which appear simultaneously at several points along the bowel. Rushes are commonly made up of several little surges and waves.

After a large rush wave passes, there are usually one or more small "scavenging waves" which serve to empty the bowel. Sometimes there are also little surges running orad for a short distance.

Disturbances commonly appear in a segment of bowel from three to ten seconds before a rush arrives. They consist usually of increases in tonus and activity, but occasionally some inhibition can be detected.

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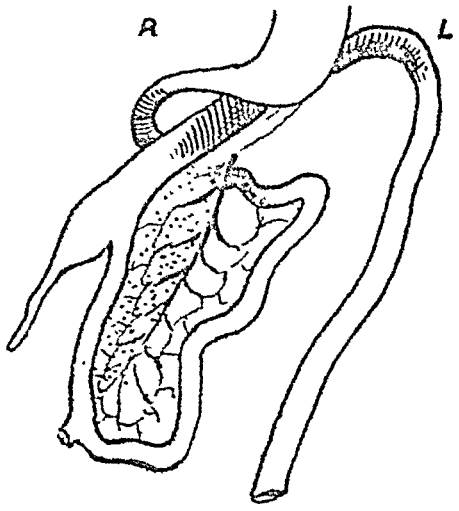


Fig. 3. The rotation of the midgut is completed, the different portions of the intestinal tract are about in their permanent positions.

short distance from each other forming the "duodeno-colic isthmus."

During the further growth of the midgut, the abdominal cavity becomes too small to harbor all the fast growing intestinal loops and a temporary physiological umbilical herniation is formed containing a large portion of the midgut. This is the situation about at the tenth week and within the next week the following important development occurs: The small intestines reenter the abdominal cavity beginning from the proximal (duodenal) end and followed by the distal loops (jejunum and ileum) and finally by the cecum and ascending colon. The loops slide behind the mesenteric artery (see Fig. 2), thereby forming the duodeno-jejunal flexure. The upper jejunal loops occupy the left upper abdomen pushing the splenic portion of the colon upwards and towards the left side into its permanent position. After the lower ileal loops reenter, the cecum and ascending colon are placed in the right upper quadrant (see Fig. 3).

During the late months of pregnancy the cecum reaches its permanent position in the right iliac fossa by descent and longitudinal growth. All portions of the colon then become fixed in position by fusion of the mesenteric folds with the posterior peritoneum.

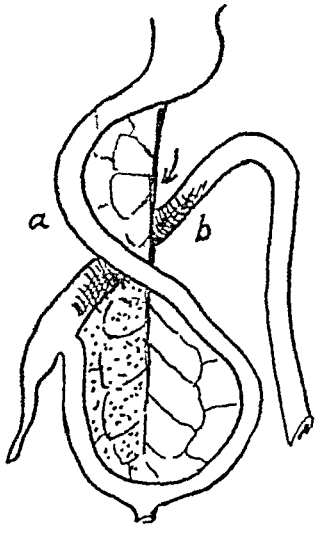


Fig. 4. Reversed rotation. The lower ileum and proximal colon reenter first thereby rotating the midgut in the reversed direction. The duodenum (a) is in front, the transverse colon (b) is behind and trapped at its middle (arrow) by the stem of the superior mesenteric artery.

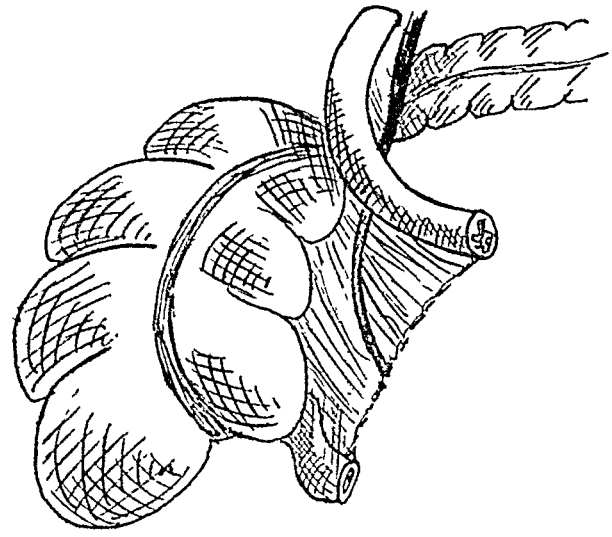


Fig. 5. Operative findings in a case of reversed rotation which lead to acute intestinal obstruction. The findings correspond exactly with the anatomical situation in Fig. 4. Note the dilatation of the proximal and the collapse of the distal colon. (after GARDNER and HART. *Arch. of Surg.*, 29:952, 1934).

ANOMALIES OF ROTATION

A review of the literature reveals that practically all the abnormalities occur in the midgut, while malformations in the foregut and hindgut are considered as extremely rare. However, not as much attention has been paid to these portions and it is possible that further study will reveal changes corresponding to those in the midgut.

Disturbances in the normal development of the mid-

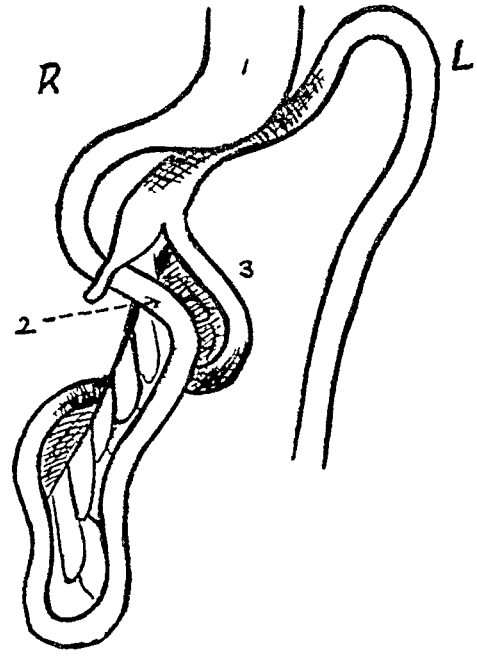


Fig. 6. Malrotation. The proximal and the distal part of the midgut reenter the abdominal cavity at the same time, the former in front, the latter behind the artery. The duodenum (2) and the lowermost loop of the ileum (3) are placed side by side. The cecum is in a subpyloric position.

Gastric samples: The Rehfuss method of extraction was employed. Pepsin was determined in samples obtained 15, 75 and 120 minutes, respectively, after the ingestion of the meal. Free HCl and total acidity were also titrated.

TABLE I

Typical normal response

Time	Free HCl	Pepsin	Free HCl	Pepsin
min. after meal	c.c. N/100 per c.c.	units per c.c.	c.c. N/100 per c.c.	units per c.c.
	Plain Meal		Meat Meal	
15	0	70	4	700
30	10		10	
45	24		14	
60	32		18	
75	30	660	28	1000
90	20		30	
105	30		36	
120	26	1000	20	1200

Tests were performed on 15 individuals, comprising several normal persons and a number suffering from gastric disorders. Twelve pepsin determinations were made in each case, a total of 180 determinations. They have been divided according to their free HCl secretory curves into four groups:

1. Euchlorhydria (free HCl 20-40).
2. Hypochlorhydria (free HCl below 20).
3. Achlorhydria and Achylia (no free HCl).
4. Hyperchlorhydria (free HCl above 40).

TABLE II

Case of hypochlorhydria. Patient J. D.

Time	Free HCl	Pepsin	Free HCl	Pepsin
min. after meal	c.c. N/100 per c.c.	units per c.c.	c.c. N/100 per c.c.	units per c.c.
	Plain Meal		Meat Meal	
15	0	1000	0	300
30	0		0	
45	0		6	
60	0		6	
75	18	800	24	800
90	10		26	
105	16		36	
120	30	1300	32	2400

In the normal or euchlorhydria group, the first samples, obtained 15 minutes after ingestion of the test meal, were relatively low in peptic power, although all were above 300 units. A marked rise then occurred, the 75 minute samples showing a content of over 1000 units in most cases. This high peptic power was usually maintained to the end of the two hour period, but when it varied much the variation as a rule paralleled the fluctuation of the free HCl. The meat meal usually produced a higher pepsin content than the meatless meal. This is well shown in the typical experiment summarized in Table I.

TABLE III

Case of achylia. Patient R. M.

Time	Free HCl	Pepsin	Free HCl	Pepsin
min. after meal	c.c. N/100 per c.c.	units per c.c.	c.c. N/100 per c.c.	units per c.c.
	Plain Meal		Meat Meal	
15	0	20	0	10
30	0		0	
45	0		0	
60	0		0	
75	0	100	0	Pepsinogen 4 Pepsin 8
90	0		0	
105	0		0	
120	0	8	0	40

In the hypochlorhydria group the peptic activity was not diminished as a rule. Although the free HCl was minimal in amount, there was often seen a rough parallellism between the free HCl and the amount of pepsin present. (See Table II).

The achlorhydria and achylia group consisted of cases of mucus gastritis, atrophic gastritis, and one case of pernicious anemia with achylia. It is noteworthy that an absence of pepsin was seldom, or never seen, even in cases showing no free HCl throughout the two hour period. A typical example is shown in Table III.

TABLE IV

Case of hyperacidity. Patient J. R. M.

Time	Free HCl	Pepsin	Free HCl	Pepsin
min. after meal	c.c. N/100 per c.c.	units per c.c.	c.c. N/100 per c.c.	units per c.c.
	Plain Meal		Meat Meal	
15	0	330	30	600
30	54		38	
45	45		30	
60	60		43	
75	56	2000	34	2000
90	56		40	
105	70		40	
120	50	2000	30	2000

There are several points which deserve some empha-

sis. In the first place, the concentration of pepsin is independent of that of free HCl. However, in any given case the two values usually run more or less parallel. Secondly, pepsin or pepsinogen was demonstrable in nearly every sample tested, even when no HCl was present. Rockus, Bank, and Willard (9), after injecting histamine, found "gastric rennet" (which must now be considered to be pepsin) and no HCl present in seventeen out of sixty-four cases. These they term "true achlorhydrias," instead of the more usual expression "true achylias." They also conclude that "the secretion of gastric enzymes apparently persists in many stomachs after acid secretion has stopped." Thus the usually accepted distinction between achylia and achlorhydria becomes more difficult to make. An achlorhydria has usually been considered a case in which HCl is lacking but in which the enzymes may be present. In achylia, on the other hand, neither acid nor enzyme is present, according to the usual classification. Now, if the enzyme is seldom, if ever, completely absent—as appears to be the case when our delicate method is employed—then either the term achylia must be dropped, or a new definition be found. The explanation of the persistence of pepsin lies, of course, in the evident fact that although the parietal cells may be destroyed some chief cells continue to be active even in advanced cases of "achylia."

The addition of cooked meat to the test-meal produced, in all cases except the achylias, an increased content of pepsin in the gastric juice. Many substances, including raw meat, are known to increase the flow of gastric juice when introduced into the stomach. In our experiments, however, is seen a different phenomenon, i.e., a change in the concentration of the enzyme as a result of a definite stimulus, presumably chemical in nature.

SUMMARY

1. This method is simple, accurate and rapid. It can easily be used as an office procedure.

2. It is extremely sensitive, as small amounts of pepsin may be detected.

3. Peptic activity apparently seems to run parallel to HCl secretion in all cases except those in the Achylia group.

4. In Achylia gastrica, it seems that pepsinogen or pepsin is still secreted despite the fact that HCl is not present.

5. Meat usually produces a definite increase in peptic activity in all groups except the achylias.

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Abnormalities of the Rotation of the Midgut: a Report of Four Cases*

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THE faulty rotation of the midgut, leading to abnormal position of the intestines, is a congenital anomaly due to a disturbance in the normal embryological development of the intestinal tract. The thorough knowledge of its different variations is not of a mere theoretical interest but of great practical consequence since grave complications may occur at any time. The previous knowledge of the anatomical situation may clear up indistinct clinical pictures and may facilitate necessary interventions or avoid unnecessary operations. The only means of diagnosing the condition before operation is by roentgenologic study with the exception of the newborn, in whom the anomaly may be suspected from the clinical course.

While the anatomical condition was known to the anatomists for about a hundred years, the first correct diagnosis on the living patient before operation was made only as recently as 1924 by Altschul (1). The clinical picture produced by the abnormal rotation of the midgut ("mesenterium commune" of the European

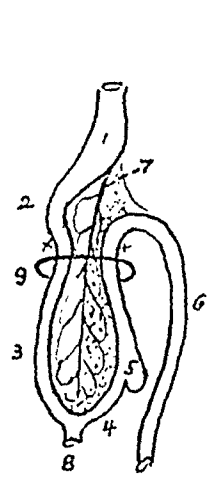


Fig. 1a. Embryo of 8 weeks. Normal development, first rotation completed. (1) stomach. (2) duodenum. (3) midgut, prearterial portion. (4) midgut, postarterial portion. (5) cecum. (6) descending colon. (7) stem of the superior mesenteric artery. (8) omphalomesenteric duct. (9) umbilicus. xx duodeno-colic isthmus.

*From the roentgenological service of Dr. Max Cohn of the Mount Sinai Hospital in Chicago.
Submitted October 21, 1936.



Fig. 1b. Anatomical situation in a case of an adult with a nonrotation of the midgut. Note the lack of the duodeno-jejunal flexure, the position of the small bowel within the right and the large bowel within the left side of the abdomen, the crossing of the last loop of ileum from the right to the left and the position of the appendix within the left lower quadrant. (after GREEN. *Surg. Gyn. Obstr.*, 53:737, 1931).



Fig. 1c. X-ray picture of Case 1. It corresponds almost exactly with the anatomical picture Fig. 1b. (a) stomach in normal position. (b) small bowel within the right side. (c) crossing of the last loop of ileum. (d) large bowel within the left side. Cecum and ileocecal region in the left lower quadrant between c and d. The arrow points to the duodenum which leads directly to the rightsided upper jejunal loops.

literature) varies from very slight abdominal discomfort to true acute intestinal obstruction, therefore it is essential to be familiar with all its anatomical features and clinical symptoms. Although I believe, that the condition is not extremely rare, a review of the world literature has revealed only about 120 cases. It is probable, that a considerable number of cases have been observed but have not been reported.

EMBRYOLOGY

The exact knowledge of the embryological situation is indispensable and can be best obtained from the classical description by Norman Dott (8). In 1934, Gardner and Hard (10) published an extensive and beautifully illustrated paper on this subject.

At the 5th week of embryonic life the intestinal canal is a longitudinal tube fixed to the posterior wall of the abdominal cavity by the mesenteric plate, both being oriented in the vertical direction and in the sagittal plane. At this time the intestinal canal is subdivided into (1) foregut supplied by the celiac axis, (2) midgut supplied by the superior mesenteric artery and (3) hindgut supplied by the inferior mesenteric artery. From the foregut is derived the abdominal part of the esophagus, the stomach and the duodenum down to a point just below the papilla of Vater. The midgut forms the distal portion of the duodenum, the small intestines and the large bowel as far as the middle of the transverse colon. From the hindgut the rest of the large bowel is derived (see Fig. 1a).

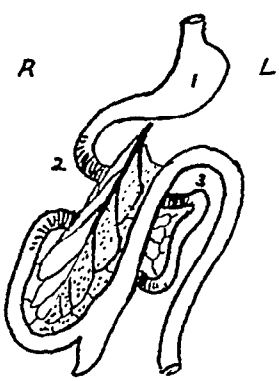


Fig. 2. Normal development about at the 10th week. The proximal jejunum reenters the abdominal cavity sliding behind the stem of the mesenteric artery. The duodeno-jejunal flexure is formed. (1) stomach. (2) duodenum. (3) duodeno-jejunal flexure.

At the middle of the midgut the omphalomesenteric duct is found and opposite its origin the superior mesenteric artery divides into its terminal branches. The midgut and its mesentery are divided into the prearterial and the postarterial segment. Distally from the middle of the gut a bud is formed for the later development of the cecum. The midgut grows much faster than the other portions of the intestinal tract, especially at its prearterial segment which forms all the loops of the small bowel except the lower ileum.

With the so called first rotation the midgut and its mesentery are placed from the sagittal into the frontal plane thereby locating the duodenum and small intestines into the right side, and the colon into the left side of the abdominal cavity (see Fig. 1a). At the same time the foregut performs a rotation whereby the pyloric portion of the stomach is directed towards the right side, the anterior wall (larger curvature) downwards and to the left, the posterior wall (lesser curvature) upwards and to the right.

The two footpoints of the midgut, located at the middle of the duodenum and the middle of the transverse colon, become fixed with the posterior peritoneum at a rather



Fig. 9. Nonrotation of the midgut (Case 4). Observation of Dr. Max-Cohn. The colon is visualized by means of a barium enema. All the typical findings of nonrotation are present.

symptoms and clinically healthy. From the papers published up to date it is not possible to get reliable information about their percentage. The anomaly is found accidentally during an abdominal operation or as a true leftsided appendicitis or as a surprise at necropsy.

Group 2. A large group of patients describe upon questioning vague gastro-intestinal symptoms such as discomfort, moderate pain, a feeling of vague pressure, belching and sometimes mild constipation. Another group complains of occasional sudden attacks of marked abdominal pain not well localized and vomiting. There are always long periods of complete health interrupted by the above reported attacks. It is not possible clinically to make the diagnosis or even to suspect the malformation. The patients report in the X-ray department with clinical diagnoses such as "possible gastric or duodenal ulcer," "rule out carcinoma" or merely "unclear abdominal complaints."

Group 3. Acute intestinal obstruction may occur at any age, cases having been reported in the first days of life and as late as 76 years. The long common mesentery is prone to form a volvulus, turns up to 450° having been described (8). Previous symptoms are present in the majority of cases but may be completely absent. One group presents symptoms from early youth — that is repeated attacks of pain with vomiting which always clear up spontaneously — the patients may be slightly underdeveloped. Obstruction occurs in adolescence particularly around the 15th to the 18th year. This history points towards malrotation or reversed rotation rather than towards nonrotation. The findings in reversed rotation show a typical location, as the obstruction is found in the middle of the transverse colon at the point where the colon is trapped behind the stem of the mesenteric artery (see Fig. 5). Patients showing their first symptoms later in adult life are usually cases of nonrotation. In all varieties cases are reported, in which operative treatment gave excellent results with complete disappearance of all the symptoms.

Group 4. High intestinal (duodenal) obstruction of the newborn in abnormal rotation becomes evident around the 3rd to the 8th day of life. The infant becomes acutely ill and vomits ½ to 1 hour after feeding. Due to the location of the stenosis below the papilla of Vater *the stomach contents are bile stained and the stools become gradually colorless.* The upper abdomen is distended, the lower scaphoid and the child looks dehydrated. Clinically differentiation from congenital atresia of the duodenum is impossible, while the differential diagnosis of pyloric stenosis and abnormal rotation of the midgut is presented in the following chart:

	onset	time betw. feeding and vomit.	gastric contents
Pyloric stenosis	3-4 weeks	a few minutes	colorless
Common mesentery	3-8 days	½-1 hour	bile stained

The majority of these cases showed adhesions between the lower duodenum and the last loop of ileum due to malrotation. Occasionally, nonrotation or reversed rotation was found. If intervention is not practised the condition is usually fatal. Operations (gastro-enterostomy) on the newborn have been reported with complete recovery. The condition is sometimes reported as "abnormal bands" at the duodenum, the underlying abnormality having escaped recognition.

ROENTGENOLOGICAL CONSIDERATIONS

Roentgenological diagnosis of abnormalities in the rotation of the midgut is very easy and is usually made at the first glance. On examination of the stomach we observe the barium passing through the duodenum filling the upper jejunal loops without forming the duodeno-jejunal flexure (see Fig. 7). The jejunal loops occupy only the right side of the abdomen, the left side remaining completely empty. In case a barium enema was given first, the colon is found within the left and middle region of the abdomen, the cecum higher or lower at the midline. Except in some very rare cases of reversed rotation, where, roentgenologically, the large bowel may appear in its normal position, with either method of examination the condition cannot be overlooked by a fluoroscopist acquainted with the abnormality. After the diagnosis is made, the following points have to be cleared up: (1) The exact variety of the malformation (nonrotation, reversed rotation, malrotation) has to be determined. (2) The lowermost loop of ileum has to be located and its position in regard to cecum and duodenum determined. (3) Cecum and appendix have to be located. In case that the large bowel is found approximately in its normal position, the relation between the duodenum (anteriorly) and the colon (posteriorly) has to be demonstrated.

From our experience it is difficult to demonstrate all points of interest on a single film, and even with a cooperative patient the results may be disappointing. The following procedure in our hands gave the best results: After the preliminary diagnosis is made, the examination is discontinued and we wait for clear



Fig. 7. Nonrotation of the midgut (Case 3). Film taken 10 minutes after administration of a barium meal permits certain diagnosis of abnormal rotation of the midgut. Note the normal position of the stomach, the lack of the duodeno-jejunal flexure and the position of the small bowel within the right side only.

gut are of three different kinds: (a) nonrotation, (b) reversed rotation, (c) malrotation.

(a) *Nonrotation* is in its essential appearance best illustrated by comparison of Fig. 1a, b and c. In the patient with this type of abnormality the portion of the intestinal tract which is derived from the midgut is found in exactly the same position as in an embryo 8 weeks of age. The typical anatomical findings are:

(1) Lack of the duodeno-jejunal flexure.

(2) Position of the small intestines in the right side of the abdomen.

(3) Position of the whole large bowel in the left side of the abdomen.

(4) Location of the appendix at the midline or in the left side of the abdomen.

(5) Crossing of the last loop of ileum over the midline from the right to the left side of the abdomen to join with the right medial border of the cecum.

(b) *Reversed rotation.* In this state the loops of the midgut reenter the peritoneal cavity in the wrong order. The postarterial segment—i.e. the ascending colon, then the cecum, then the lower ileum—enters first and is followed by the prearterial portion, thereby resulting in a rotation of the midgut which is exactly the reverse of the normal. The position now obtained is characterized by the following anatomical findings: (See Figs. 4 and 5).

(1) Position of the duodenum in front of the large bowel and the mesenteric artery, lack of duodeno-jejunal flexure.

(2) Position of the mesenteric artery in front of the colon.

(3) Circumscribed narrowing at the middle of the transverse colon which is trapped here behind the stem of the mesenteric artery.

(4) Normal position of the other portions of the intestines.

(c) *Malrotation.* This condition occurs in the cases where the prearterial and the postarterial segments reenter the abdominal cavity at the same time, the former in front and the latter behind the mesenteric artery. The characteristic *anatomical findings* are: (See Fig. 6).

(1) Position of duodenum and upper jejunal loops (prearterial segment) in front of colon and mesenteric artery.

(2) Position of the lower small intestinal loops behind the mesenteric artery as in the normal patient.

(3) Position of duodenum and terminal ileum side by side often fixed by extensive adhesions.

(4) Presence of a very long and very narrow mesenteric pedicle, on which the whole small intestines and the proximal colon (former midgut) are freely suspended.

(5) Position of the cecum in the subpyloric region.

Anomalies of the rotation of the midgut have to be strictly differentiated from situs inversus abdominalis. The latter is merely an exact reflexion image of the normal. Sandera (21) has described a very unique case of a patient in whom both conditions were present simultaneously. Familial occurrence of mesenterium commune has been reported by Spitz (23).

CLINICAL PICTURE

Considering the common underlying pathology the variety of the clinical picture is astonishing. A subdivision into 4 main groups is possible:

Group 1 shows complete absence of any clinical symptoms.

Group 2 presents gastro-intestinal disturbances of moderate degree over a shorter or longer period of time.

Group 3 presents acute intestinal obstruction.

Group 4 comprises the high duodenal obstruction of the newborn.

Group 1. There seems to be no doubt, that a considerable number of patients are absolutely free of



Fig. 8. Nonrotation of the midgut (Case 2). *All points* of interest are visualized on one film. (a) duodenum leading directly to the upper jejunal loops in the right side. (bb) last loop of ileum crossing the midline. The appendix (arrow) visualized within the left lower quadrant. The small bowel is within the right, the large bowel within the left side of the abdomen.

Proctoscopic examination was negative.

A barium enema was negative.

On September sixteenth, the blood count dropped to 2,800,000 red cells with 45% hemoglobin. The following day, a soft, transverse body, three centimeters above the umbilicus which felt like a normal, hollow viscus was noted. There was also complete papillary atrophy of the tongue. Vomiting persisted. On September eighteenth, a rather soft, not tender mass about three by two inches was felt to the right of the umbilicus and indefinitely outlined, which gave the impression of changing size and shape under examining fingers. This mass was fairly movable, and it was thought it might be distended loops of small bowel. In the next few days, this mass became much more definite and increased in size but it was still thought to be a distended hollow viscus.

On September twenty-fifth, it was concluded that with a story of evanescent tumor together with vomiting and X-ray evidence of dilated duodenum, it was most likely the lesion was an obstruction high in the intestinal canal probably in the third portion of the duodenum or upper jejunum and that exploration was advisable.

On September twenty-eighth, under gas anaesthesia, patient was operated upon by Drs. Holman and Poth. A normal appearing stomach presented. The duodenal outlines were rather indefinite at first and there was a large, soft mass in the duodenal region directed down toward the ligament of Treitz. The pancreas, kidneys, and pelvic organs were normal. The transverse colon was then delivered into the wound and after that the jejunum distal to Treitz's ligament was brought up. It was found to be quite large and thickened, about eight centimeters in diameter and contained a large, freely movable, soft mass. Further examination of the duodenum showed it to be freely movable, very large, and at its proximal third there was an invagination of the duodenum into itself. The intussusception was then reduced. At the junction between the proximal and middle third of the duodenum there was a dimpled area on the anterior surface. Examination of the biliary tract showed the common duct to be dilated and entering the duodenum distal to the point of this dimpling. The gall bladder was large but contained no stones. The duodenum was then split over the dimple and a large sessile polyp made up of multiple polypi was delivered. This was then excised, leaving a margin of about one centimeter of normal bowel entirely surrounding it. The defect in the duodenum was then closed transversely. The defect in the duodenum included about two-thirds of its circumference. The great omentum was brought up and tacked to the line of sutures to aid in preventing subsequent intussusception.

Patient was returned to the ward in good condition. She had a rather stormy post-operative course with considerable difficulty in taking her food, persistent vomiting for seventeen days postoperatively, but with a high-caloric, high vitamine diet, liver extract, frequent transfusions, glucose and salt solution, she gradually improved. However, during this period the anemia persisted, the blood ranging around 52% hemoglobin with 2,880,000 red cells. There was some generalized edema and blood proteins were found at 3.85 grams per 100 c.c.

On November twenty-fifth, she was eating quite well, the edema was decreasing, the tongue was still quite smooth, but in spite of transfusions, iron, and liver, the blood remained at about the same level, the blood proteins also remaining low. On December third, she was dismissed from the hospital on a high protein, high vitamin diet with instructions to take lextron, three pills three times per day.

In July, 1936, she was seen at the clinic; her appetite was excellent, she had gained to one hundred forty-eight pounds, and the tongue was not smooth. A blood count showed 65% hemoglobin with 3,480,000 red cells; 36% hematocrit with a diameter of 8.3 microns. The stormy and prolonged post-operative period was largely due to the complicating deficiency states following many months of poor diet.

Gross Specimen: Consists of a cauliflower-like, grey, formalin fixed tumor with a small piece of bowel well attached. The tumor measures 9 x 8 x 4 centimeters and weighs 56 grams. The surface is roughened but velvety in appearance. Cut section shows the papillomatous nature of the specimen. The bowel wall although somewhat thickened appears normal.

Histological Examination: Shows columnar epithelium with many goblet cells thrown up into the folds which radiate out from a central fibrous stalk. The epithelial cells are irregular, well circumscribed, showing no mitosis and no extension into the underlying tissue. In the submucosa are seen normal appearing Brunner's glands. The blood vessels are dilated, many of which are filled with red blood cells. There is no evidence of malignancy. The diagnosis is Papilloma, adenomatous (duodenum).

DISCUSSION

In Chart I we have tabulated the essential findings in these cases. From this review, it is evident that duodenal intussusception occurs in both males and females in an age ranging from twenty-one to seventy-five years. Symptoms were present from four to twelve months before being relieved by surgery or terminating in death. The outstanding symptom has been vomiting, occurring irregularly after meals and starting usually intermittently but becoming more frequent and more severe. Pain may or may not be present. Weakness and loss of weight are marked. Physical signs other than emaciation may be absent but the finding of a tumor in the upper abdomen, especially if it is inconstant in appearance and variable in size and shape, should make one suspect intussusception.

Of the laboratory findings, occult blood in the stools and anemia are apparently constant.

X-ray examination has so far proven disappointing primarily because the significance of the finding was not appreciated. In Kellogg's case, the barium shadow of the dilated duodenum is interrupted by a spherical mass surrounded by a ring of barium which as Kellogg (2) reports was described by Carmen as typical of tumor formation but which was interpreted in this case as obstruction due to adhesions.

In Case VII, there was abrupt termination of the barium shadow of the markedly distended loop of duodenum and yet the X-ray department reported that no pathology could be demonstrated. In their subsequent report the fact that the obstruction was inconstant made diagnosis difficult for the possibility of intussusception was not considered.

In all but one of these cases a benign tumor was the exciting factor in the development of the intussusception. Tumor of the bowel is recognized as one of the primary etiological factors in the production of intussusception in adults. Benign tumors of the duodenum account for only about five per cent of the benign tumors of the bowel. Frequently, no symptoms are produced but as reported by Balfour and Henderson (9) in a study of fourteen cases, benign tumors of the duodenum may be responsible for serious symptoms, particularly hemorrhage. Raiford (10), in a report of forty-eight benign tumors of the small intestine found ten in the duodenum. He states that "invagination seldom occurs and symptoms when present are brought on by encroachment of the tumor mass upon

working conditions. The night before the examination the patient takes one full barium meal mixed with one tablespoonful of epsom salts in order that the cecum and the appendix may be visualized. Often a good regular filling of the whole large bowel is hereby obtained. On the following morning one-third of a barium meal is administered, the passage of which is observed by repeated fluoroscopic examinations. As soon as the junction of the lowermost ileum with the cecum is visualized, another third of a meal is given, to show stomach, duodenum and upper jejunum. If necessary, the lowermost portions of the colon can be filled by a small barium enema. Repeated observations are necessary. The smaller the amount of barium given, the clearer the situation is visualized. In cases of intestinal obstruction this plan has to be changed according to the symptoms and the general condition of the patient. If the above described technique fails, it is advisable to watch the passage of a contrast meal and to give a barium enema plating the different points of interest successively.

REPORT OF FOUR CASES

Case 1. Male, age 20 years. The patient was in perfect health and without any abdominal complaints up until 3 years ago. Since then he suffered from cramplike pains in the epigastrium coming about 3 hours after meals. Occasionally the pain was present at night. Sodium bicarbonate gave immediate relief. Vomiting, belching and acid eructations were present. He also had the typical periods of freedom from symptoms experienced by the peptic ulcer patients. X-ray examination (5/7/1935) revealed an irregular and narrowed duodenal cap with a true ulcer niche at its lesser curvature towards the base. In addition we found an absence of the duodeno-jejunal flexure and in following up the case the typical picture of a nonrotation of the midgut (see Fig. 1c).

In this case all the symptoms are best explained by the presence of the duodenal ulcer, and it is reasonable to assume that the anomaly of the midgut is not responsible for the complaints of the patient.

Case 2. Female, age 41 years. The patient was in good health and without any abdominal complaints up until 4 years ago. Since that time she complained of severe cramplike abdominal pain localized in the left lower quadrant and radiating towards the back. Together with the pain tenesmus was present. While generally moderate constipation prevailed there were attacks of diarrhea. The pains were occasionally very strong and often lasted for six hours. There was no nausea, belching or vomiting nor any connection of the pain with the intake of food. Occasionally the described symptoms ceased for one or two weeks but always recurred. Hysterectomy performed 3 years ago did not relieve the symptoms. The clinical diagnosis was: Spastic colitis, malignancy to be ruled out.

X-ray examination (12/5/1935) revealed the typical picture of an abnormal rotation of the midgut. In this case it was possible to visualize all the points of interest including the filled appendix on one single film (see Fig. 8). Except for the malformation repeated examinations of the colon did not reveal any organic pathology of the colon or the appendix.

It is probable, that the rather severe symptoms of the patient were due to the intestinal malformation since clinically, surgically and roentgenologically there were no evidences of other pathology. Since the symptomatology is mainly colonic and especially since at several occasions the proximal colon seemed to be moderately widened, the possibility of a reversed rotation was seriously considered.

Case 3. Male, age 38 years. 13 years ago the patient complained of occasional epigastric distress with moderate pain occurring usually after eating. This lasted for a few months to disappear completely. For the last 5 months the above described symptoms were present but more pronounced. The patient felt nauseated but did not belch or vomit. X-ray examination (4/23/1936) (see Fig. 7) revealed a typical nonrotation of the midgut and no further intestinal pathology. The appendix was well visualized in the left lower quadrant.

As on repeated examination no further pathological findings could be demonstrated, it is probable, that the mild chronic symptoms were due to the intestinal anomaly.

Case 4. An X-ray picture of a young male patient, examined by Dr. Max-Cohn is added; it presents all the typical signs of a non rotated midgut (see Fig. 9).

SUMMARY

The embryological phases of the development of the intestinal tract are reviewed with special reference to the normal and abnormal rotations occurring in the midgut. The different clinical pictures are discussed. Mesenterium commune is not a mere abnormality, but may lead to intestinal obstruction, incomplete volvulus or to difficult diagnostic problems in case of a true leftsided appendicitis. A roentgenological technique adequate to demonstrate the condition is described. A report of four observations is given.

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Further Refinements in the Method of Administering Colon Bacillus Vaccine Therapy, and in the Therapeutic Use of Sodium Ricinoleate

(As Related to Chronic Functional Diarrhea, Chronic Headache, Chronic "Toxic Vertigo" and the "Unstable Colon")*

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INTRODUCTION

IN an earlier publication (1), the authors presented in comprehensive form the various indications and contra-indications for, and the limitations of, colon bacillus vaccine therapy. The methods of preparation and administration of detoxified B. coli vaccine were outlined. In four groups of cases, the therapeutic results definitely due to colon bacillus vaccine therapy were tabulated statistically. These four groups included, (1), the chronic functional diarrheas, (2), chronic headaches of the type associated with chronic constipation or colon distress, (3), cases of "toxic vertigo," and, (4), a group of "unstable colon" (non-ulcerative colitis) cases. Convincing results were obtained from B. coli vaccine therapy in groups of such patients whose symptoms had not disappeared following employment of the usual therapeutic measures. From these and other observations, the conclusion was reached that colon bacillus vaccine therapy, if judiciously used in properly selected cases, with avoidance of overdosage, constitutes a valuable therapeutic aid. Although the various observations and deductions outlined in the previous comprehensive publication will not be reviewed in this publication, one should be thoroughly conversant with them before employing this type of vaccine therapy.

It is important to emphasize that, in the above four related groups of cases, it is customary after diagnostic study to institute first a comprehensive plan of therapy. Colon bacillus vaccine therapy is reserved for those patients who have not obtained a satisfactory result from the above therapeutic program. The comprehensive plan has consisted of, (1), eliminating, as far as possible, the various etiological factors contributing to nervous tension, (2), the correction of any other faulty habits, (3), obtaining a diet diary from the patient, which permits the elimination of probable aggravating articles of food, and the provision of adequate vitamines and a proper balancing of the diet, (4), physiological regulation of the bowels, (5), the temporary use of a simple nerve sedative (if indicated), and, finally, (6), the therapeutic use of sodium ricinoleate ("Soricin"). In the "unstable colon" group of cases, the use of belladonna or atropine for the symptomatic relief of colon distress no longer is necessary, except in occasional cases.

Since the last publication, two important advances in the therapeutic management of the four above-mentioned groups of cases have been made. First, the routine use of sodium ricinoleate in larger doses than formerly used has proven to be of great therapeutic aid in all four types of cases, and has reduced definitely the number of such individuals requiring colon bacillus vaccine for complete relief of symptoms. In the second place, in the remaining group of patients who do need colon bacillus vaccine for complete relief, in addition to sodium ricinoleate and the comprehensive program, the occurrence of occasional, disagreeable, temporary reactions to B. coli vaccine has been eliminated largely by the refinements in the method of its administration outlined below.

SODIUM RICINOLEATE THERAPY

As emphasized above, sodium ricinoleate has proven to be of great aid in the treatment of these four related groups of cases. The new 5 grain, enteric-coated "Soricin" tablets are preferable, for several reasons, to the "Soricin" capsules formerly employed. The daily dose has been increased over that formerly suggested, and varies between three and six "Soricin" tablets each day. Some patients do obtain complete relief of symptoms from 1 tablet t.i.d.a.c. Others obtain only partial relief of symptoms from this dose, but secure complete relief promptly when the dose is doubled to 2 tablets t.i.d.a.c. Only very occasional patients develop slight, transient, intestinal "uneasiness" from 6 tablets per day. It is recommended that the routine dose be 6 tablets per day, as advised by Schiff (2). In the milder cases, this dose can be reduced to 3 tablets a day after several weeks. In the moderate and severe cases, the larger dose of 6 tablets per day should be maintained. If one wishes to obtain therapeutic results from "Soricin" which persist after the "Soricin" is discontinued, it is important to continue its administration for a period of four to six months—or occasionally longer. Only good effects from this practice have been noted. Sodium ricinoleate should be used almost routinely in the above related groups of cases.

COMBINED USE OF SODIUM RICINOLEATE AND B. COLI VACCINE

In obstinate cases, the best therapeutic results are obtained by the addition of colon bacillus vaccine therapy to "Soricin" therapy. In those occasional cases, within the above four groups, in which a combination of these two therapeutic agents has not re-

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lieved the symptoms, one should suspect either the persistence of an important, uncontrolled, nervous tension factor, or else an early, undiagnosed organic basis for the apparently functional symptoms.

REFINEMENTS IN ADMINISTRATION OF B. COLI VACCINE

Further important refinements in the method of administration of B. coli vaccine have been developed. These improvements have resulted in an almost entire elimination of the temporary but disagreeable reactions which formerly followed colon bacillus vaccine injections in certain individuals with low tolerance.

SKIN TESTS

The first refinement has consisted in omitting the former practice of doing a preliminary skin test with concentrated, unaltered colon bacillus vaccine, before starting the therapeutic course of injections. Formerly, when one immediately gave a skin test with a one billion, or a .200 million concentration of vaccine, there were occasional cases in which there was a disagreeable temporary reaction. Such reactions do not occur if one starts with an initial, more dilute, therapeutic dose of detoxified vaccine. Moreover, as noted in the previous publication, 99% of all patients presenting the four types of conditions referred to above exhibited a positive skin reaction with a one billion concentration of colon bacillus vaccine. Therefore, a preliminary skin test with a concentrated vaccine is no longer considered necessary nor indicated.

INITIAL DOSE OF VACCINE

The second refinement has involved the reduction of the initial therapeutic dose of vaccine from 2 minims of a 50 million or 250 million concentration to 2 minims of a 5 million concentration. By this change of proceedure, one almost completely eliminates the former disagreeable, temporary reactions, which occurred occasionally with the larger initial dose. It is true that, in case patients have an initial tolerance for the higher concentrations of colon bacillus vaccine, the prompt and dramatic symptomatic relief often seen in such cases will be postponed if one starts with the more dilute vaccine. It is also true that, when starting with the 5 million dilution, several more injections are added to the usual total course. Nevertheless, it is felt that the advantage of almost eliminating the disagreeable reactions, in the occasional patients with minimal tolerance, more than justifies this reduction in the initial dose.

CRITERIA FOR DETERMINING SUBSEQUENT DOSES OF VACCINE, AND METHOD OF RECORDING DATA

The third refinement has consisted in increasing subsequent doses of vaccine more gradually. As emphasized and more fully elaborated in the earlier publication, each subsequent increase of dose, after the initial injection, should be determined by the patient's response to the last injection, and should be individualized. Two items of information should be obtained from the patient just prior to each injection, as a necessary basis for determining the size of each successive dose, viz., (1), whether any temporarily disagreeable reaction or symptoms occurred within 3-24 hours after the last injection, e.g., fatigue, malaise, headache, generalized muscle-aching, transient joint pains, or slight aggravation of the symptoms for the relief of which colon bacillus vaccine has been given; and, (2), whether the patient noted improvement or disappearance of the symptoms, following the dose last administered. If any transient reaction occurred, its character and degree should be noted. The information relative to improvement and reaction, whether positive or negative, following the last injection, should be recorded in separate columns, following columns marked off for the date and dose of each vaccine injection, upon a "vaccine memo sheet." This information should be kept as a permanent record, and the data recorded each time the patient is seen for vaccine injections. For, such data are invaluable in determining the optimum subsequent dose. Only by thus individualizing each dose can disagreeable reactions be avoided.

A slight, transient reaction, lasting only a few hours, and consisting usually of slight fatigue or malaise, is not a contra-indication to a moderate increase of dose at the time of the next injection. Reaction symptoms will be noted only occasionally with the method now employed for increasing dosage; and usually only the improvement or disappearance of symptoms will be observed. On the other hand, if reaction symptoms after any injection are pronounced, or if they persist several days, they not only contra-indicate any increase of dose at the next injection, but definitely indicate a decrease of dose, as compared with the last injection. Even more important than this, such symptoms also indicate that the time of administering the next dose should be postponed until the patient has fully recovered from any reaction. In the rare case in which a certain dose of vaccine temporarily aggravates the symptoms for the relief of which the vaccine is given, a definite and appreciable overdose has been given, viz., a dose in excess of the tolerance of this patient at the time of this injection.

It must be emphasized that B. coli vaccine, in large doses, is much more prone to produce disagreeable reactions than the vaccines of the pyogenic bacteria, for example. If one keeps this fact in mind, and starts with appreciably smaller doses of B. coli vaccine, such reactions usually will be avoided. On the other hand, it is equally important, in the case of those patients who have shown good tolerance for the smaller and medium-sized doses of B. coli vaccine, to gradually but steadily increase the dose to a reasonable maximum (tolerated) dose, if the best and most lasting therapeutic result is to be obtained. Patients who tolerate the larger doses usually obtain the best therapeutic results.

Until one has had experience with this type of vaccine therapy, the maximum dose of B. coli vaccine which may be used safely should not exceed 15 minims of a 250 million concentration. There are occasional patients with an unusually high tolerance who will benefit by more lasting results from the use of a 1 billion concentration. However, it is never advisable, in the opinion of the authors, to increase the dose beyond 8 minims of a 1 billion concentration; and the cases for these larger doses must be selected with care.

AVERAGE RATE OF INCREASE OF DOSE, AND METHOD OF VACCINE ADMINISTRATION

Although no sterotyped schedule of increase of dose should be followed, for the reasons specified above, the

following plan represents about the optimum rate for a patient with average tolerance for B. coli vaccine. Such a schedule is as follows, viz., 2 minims of a 5 million concentration intradermally, 6 minims of the 5 million concentration intramuscularly, 2 minims of a 50 million concentration intradermally, 6 minims of the same concentration intramuscularly, 2 minims of a 250 million preparation intradermally, and then 4 minims, 6 minims, 8 minims, 10 minims, and 12 minims intramuscularly of the 250 million concentration. Some patients do not tolerate this maximum dose. Others tolerate and should receive more. The above average course totals 10 injections. In occasional individuals, it may be necessary to reduce, rather than increase, the second dose, because of poor individual tolerance. Such patients usually do not benefit as much from the vaccine as those who tolerate it well.

The small doses of 2 minims of increasing concentrations, in the early part of the course, are best given intradermally as "desensitizing" doses. The doses of larger volume should be given intramuscularly and slowly into the deltoid or thigh muscles. One should not inject this type of vaccine either subcutaneously or intravenously. The possibility of unintentional intravenous injection can be avoided by pulling very gently upon the plunger of the syringe after introducing the needle into the muscle. After the intramuscular injections, massage at the site of injection tends to reduce subsequent local soreness—especially with the larger doses.

OPTIMUM INTERVAL BETWEEN VACCINE INJECTIONS, AND DURATION OF VACCINE THERAPY

The average optimum interval between successive vaccine injections is about 4 days, as recommended in the previous publication. If any appreciable reaction should occur after any injection, the interval before the patient receives another injection should be lengthened to 7 days, or more. In such an instance, the patient should have at least 2 really "good days," with complete absence of the reaction symptoms, before receiving the next injection. If one is giving unusually small doses, e.g., at the beginning of a course of treatment, and the patient is much improved for 1 or 2 days after the injection, with return of symptoms on the second or third day, the interval between injections should be shortened to 2 days, or the dose should be increased more rapidly. In fact, when giving very small doses, e.g., when using a 50 thousand dilution, the regular administration of the vaccine every 2 days, instead of every 4 days, is usually tolerated and produces more rapid results. If tolerated, the results are likely also to be more effective. Occasional patients tolerate these small injections every day.

Inasmuch as the main limitation of any type of vaccine therapy resides in the fact that its effect does not persist indefinitely, it is often advisable to continue one injection a month for the better part of a year, after completing the regular course of about ten injections. This is especially true in obstinate cases, not relieved by other types of therapy, that have obtained particularly gratifying results from B. coli vaccine. In such instances, the subsequent monthly dose should be maintained at a level of 50% to 100% of the last, maximum dose tolerated during the regular course of injections. A recurrence of symptoms can almost always be prevented in this manner. Such a plan avoids the necessity for a second complete or intensive course of vaccine therapy 4-6 months after the first course, when symptoms return in some cases. Occasional obstinate cases have been noted, whose symptoms have started to return in mild form as early as 3 weeks after the regular course of vaccine therapy. Such patients usually have chosen to come in for a vaccine injection every 3 weeks, instead of waiting for a longer interval to expire. In this manner, they are able to remain essentially symptom-free. On the other hand, in other patients, a single course of 10 vaccine injections, without any subsequent injections, has seemed to break a vicious circle, and the patients have remained symptom-free indefinitely. As yet, no method has been evolved to prognosticate, in the individual case, which patients will obtain relief for a long time, and which only temporary relief, following the first course of vaccine therapy.

DILUTIONS OF VACCINE NEEDED

The five following concentrations of detoxified colon bacillus vaccine are needed, as a minimum, to carry out the idea of a gradual increase of the dose for individuals with different tolerance, viz., bottles of 50 thousand, 500 thousand, 5 million, 50 million, and 250 million organisms per c.c. respectively. (In occasional cases, one will need a 5 thousand or a 1 billion concentration). With such an assortment of concentrations, it is possible early in the course of treatment to individualize the dose to the tolerance of each patient and to increase the dose as gradually or rapidly as indicated.

SUMMARY

(1) In an earlier publication, the authors presented the various indications and contra-indications for, and the limitations of, colon bacillus vaccine therapy. The therapeutic results definitely due to B. coli vaccine, in the four related groups of cases, were tabulated statistically. This evidence indicated that colon bacillus vaccine constituted a valuable therapeutic aid in a properly selected group of cases, in which supplementary aid was needed. The methods of preparation and of administration of detoxified B. coli vaccine were outlined.

(2) During the past two years, further experience with sodium ricinoleate ("Soricin"), using larger doses of 10 grains t.i.d.a.c., has demonstrated its great value in the four related groups of cases relieved by colon bacillus vaccine. The routine use of "Soricin," as one feature in the preliminary comprehensive program of therapy for these four groups of cases, has definitely reduced the number of cases requiring the addition of B. coli vaccine for relief. And yet, a definite group remain who need colon bacillus vaccine for complete and satisfactory relief.

(3) The occurrence of occasional, disagreeable, temporary reactions to colon bacillus vaccine, in patients with unusually low tolerance, has been largely eliminated by the following further refinements in the method of its administration.

(a) The first refinement has consisted in the discontinuance of doing a preliminary skin test with concentrated colon bacillus vaccine.

(b) The second refinement has involved the reduction of the former initial therapeutic dose of vaccine

of 2 minims of a 50 million or a 250 million concentration to 2 minims of a 5 million concentration.

(c) The criteria for determining the size of each, subsequent, optimum dose of vaccine have been discussed in detail. The size of each dose must be individualized to the patient. Prior to each injection, it is essential to determine, (1), whether any temporarily disagreeable reaction occurred following the last injection, and if so, its degree, type and duration, and, (2), whether definite improvement or disappearance of symptoms occurred following the last injection. These facts should be recorded upon a "vaccine sheet" in the history of the patient. The determination of the optimum dose each time is essential for the best therapeutic results.

(d) Although no stereotyped schedule of increase of dose can be followed, the schedule or rate of increase suitable for a patient with average tolerance for B. coli vaccine has been outlined in detail. The optimum route for colon bacillus vaccine injection has been discussed.

(e) The usual optimum time interval between vaccine injections and the indications for increasing or decreasing this interval have been reviewed.

(f) The various concentrations of colon bacillus vaccine, actually needed for the practical administration of this type of therapy, have been specified.

(4) The proper selection of cases for colon bacillus vaccine therapy, and the careful determination of the proper dose of vaccine at the time of each injection, constitute the two most essential requirements for successful results from B. coli vaccine therapy.

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Infant Feeding---Individualized vs. Routine*

By

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MILK constitutes the basis of infants' feedings. Proper choice of the milk suited to the particular infant is indispensable in successful infant nutrition. The great variety of milks available make such a choice difficult in the individual infant because of unnecessary empiricism in practice. More stress has been placed upon the various milks and their properties than on infants and their tolerance. Nutritional knowledge has advanced sufficiently to adapt effectively the required type of milk to the individual infant rather than the infant to the milk.

The type of milk selected requires modification, the procedure of choice depending upon the infant. The resulting formula may meet all the nutritional needs of the infant and yet be unsuited to his digestive tolerance. The theoretical goal in nutrition is the same for all infants but the methods of attaining it necessarily differs with each infant. Goal and method are not only necessary but inseparable in effective infant feeding. Thus, there can be no single formula for the universal feeding of infants. The percentage composition of cow's milk mixtures, imitating breast milk, becomes less important than the behavior in the infant's stomach. We have studied the response of various methods of feeding in terms of the infant's constitution as a more physiologic basis for determining the type of formula indicated.

PLAN OF INFANT FEEDING STUDY

Comparative studies of "standard formulae" prepared from various types of milk were made on infants during the first three months of life. The newborns on the service were maintained from birth with the hydrating solution given at two hour intervals throughout the twenty-four hour cycle and put on the formula under study on the second day of life. An effort was made in each case to have the infant nurse and the breast-fed infants were used as controls. Despite the willingness of most mothers to nurse their babies and our insistence in favor of breast feeding, less infants were nursed than is considered good practice. Although theoretically tuberculosis in the mother is the only contraindication to nursing, actually we have found severe postpartum disturbances affecting the mother physically and tempermentally to an extent that made nursing very trying. Breast pumps were tolerated for short periods and manual stripping was rejected by many mothers. Whatever the maternal condition the baby was weaned if the quantity of breast milk was less than an average of two ounces per feeding after the first fortnight.

Weaning during the newborn period was instituted for very definite indications and not for the purpose of these studies. Many of the infants included in the data nursed for a number of days during which time the intake of the special formula was relatively small. But during the baby's stay in the nursery the intake of the milk mixture was gradually increased until the formula under study comprised the total day's feeding. The infants' progress was under the supervision of research dietetians, Misses Cummings and McMahon and the technical data under Miss Pugsley, all devoting full time to these nutritional studies.

Over fifty well newborns were observed serially on each formula—fresh, powdered, evaporated and acid milks with breast milk as the control. Careful records were made of the physical status and functional response to the particular feeding. This was continued at home after the babies were discharged from the nursery and observed subsequently at weekly inter-

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vals in a well-baby unit where clinical and laboratory examinations were made. Those infants whose mothers failed to keep appointments were followed up at home by one of the dietetians. The mother was provided with the special milk used for the infant's formula

fants were maintained on a whole milk mixture for three months. It consisted of boiled whole milk with 10% added carbohydrate. The formula was started the second day of life in well newborns with a birth weight over six pounds. Although seven of the group studied had difficult deliveries

Comparative results on routine and individual formulae

	Breast Milk	Whole Milk Formula	Diluted Milk Formula	Evaporated Milk Formula	Powdered Milk Formula	Acid Milk Formula	Individualized Formula
Age of Infants (Wks.)	1 - 12	1 - 12	1 - 12	1 - 12	1 - 12	1 - 12	1 - 12
No. Cases	55	54	59	58	60	56	50
Difficult Deliveries	5	7	3	6	5	7	4
Duration of Feeding (Days)	85	80	82	86	85	88	85
Supplements	OJ&CLO	OJ&CLO	OJ&CLO	OJ&CLO	OJ&CLO	OJ&CLO	OJ&CLO
Av. Vol./Feeding (Ozs.) 1 mo.	(3.8)	4.0	4.2	4.2	4.1	3.8	4.4
2 mo.	—	5.2	5.4	5.0	5.1	5.3	5.5
3 mo.	—	6.0	6.5	6.1	5.9	6.2	6.5
Av. Vol./Day Feedings (Ozs.) 1 mo.	(22)	24	25	25	24	22	26
2 mo.	—	26	27	25	26	26	27
3 mo.	—	30	32	31	29	31	33
Av. Intake Cals./Lb./Day	(56)	60	52	66	60	67	70
Av. Gain Wt. Ozs./Wk.	6.9	6.0	5.9	7.1	6.4	7.1	7.3
Av. Gain Ht. (Mo.)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Av. No. Stools/Day	2.5	3.3	2.5	2.6	2.4	2.7	2.6
% Digestive Disturbances	8	24	12	9	11	10	2
% Infections	7	9	5	8	10	6	8
% Successful Feeding	90	70	85	88	86	88	95

thus insuring constancy of product and of cooperation. Only normal well infants were included in this series. It is the first three months of the feeding progress of these infants that concerns this report.

ROUTINE FEEDING OF "STANDARD" FORMULAE IN WELL INFANTS

I. *Control Series.* Fifty-five normal infants were maintained exclusively on breast milk for three months. The breast feeding was started five hours after birth in newborns with a birth-weight over six pounds. Although five of these newborns had difficult deliveries they showed no post-natal manifestations. Orange juice and cod liver oil were introduced the third week. The orange jucie was first given half strength and gradually increased so that two ounces were given by the end of the first month. The 10 D cod liver oil was given five drops a day increasing it gradually until each infant received one teaspoonful a day. The average volume intake was 3.8 ounces per feeding during the first month, subsequent amounts not being determined. Indeed it was difficult to obtain a sufficient number of weighings during the first month to estimate the average volume intake, the accuracy is therefore indetermine for comparison with the equivalent values for artificial feedings. The average volume intake consumed during the twenty-four hour cycle was accordingly 22 ounces. The average caloric intake was about 56 calories per pound per day. The average gain in weight was 6.9 ounces per week and the average gain in height one inch per month. The average number of stools was 2.5 per day. Three of the infants developed transient upper respiratory infections; four had alimentary disturbances, i.e., one vomited, one had colic and two developed diarrhea.

Series II. Whole Milk Formula. Fifty-four normal infants were maintained on a whole milk mixture for three months. It consisted of boiled whole milk with 10% added carbohydrate. The formula was started the second day of life in well newborns with a birth weight over six pounds. Although seven of the group studied had difficult deliveries there were no post-natal manifestations. Orange juice and liver oil were introduced the third week. The orange juice was first given half strength and increased gradually so that two ounces were given by the end of the first month. The 10 D cod liver oil was offered five drops a day increasing it gradually until the infant received one teaspoonful a day. The formula was made up for twenty-four hours and divided into six feedings given at four hour intervals during the first month and subsequently into five feedings. The amount offered at each feeding was slightly above that usually taken by infants at each age level.

The average volume consumed by an infant was 4.0 ounces per feeding during the first month, 5.2 during the second and 6.0 during the third month, the average volume for the total day's feeding being 24, 26 and 30 ounces respectively. The average caloric intake was about 60 calories per pound per day. The average gain in weight was 6.0 ounces per week and the gain in height was 1 inch per month. The average number of stools was 3.3 per day. There were three cases of upper respiratory infection, one furunculosis and one pyelitis. But thirteen infants showed other disturbances i.e., three vomited, three had colic, one had diarrhea, four were severely constipated, one developed eczema and one had pyloric stenosis.

The distribution of alimentary upsets was not uniform at each age level, the greatest proportion being during the first month and the least during the third month: 36% during the first month, 24% during the second and 11% during the third month with an average of 24% for the entire period. Several infants with limited digestive capacities were eliminated from this study during the first month. The most striking feature was the correlation between alimentary tolerance and body build. About 80%

who showed digestive disturbances were of the lateral type. Apparently the majority of infants of linear body build are able to take undiluted boiled whole milk in amounts adequate to satisfy the appetite without revealing intestinal disturbances.

Series III. Diluted Milk Formula. Fifty-nine normal infants were maintained on a diluted milk formula for three months. It consisted of boiled half-strength milk with 10% added carbohydrate. The formula was started the second day of life in well newborns with a birth weight over six pounds. Although three of the group studied had difficult deliveries there were no post-natal manifestations. Orange juice and cod liver oil were introduced the third week. The orange juice was first given half strength and increased gradually so that two ounces were given by the end of the first month. The 10 D cod liver oil was offered five drops a day increasing it gradually until the infant received one teaspoonful a day. The formula was made up for twenty-four hours and divided into six feedings given at four hour intervals during the first month and subsequently into five feedings. The amount offered at each feeding was slightly above that usually taken by infants at each age level.

The average volume consumed per infant was 4.2 ounces per feeding during the first month, 5.4 during the second and 6.3 during the third month, the average volume for the total day's feeding being 25, 27 and 32 ounces respectively. The average caloric intake was about 52 calories per pound per day. The average gain in weight was 5.9 ounces per week and the average pain in height was one inch per month. The average number of stools was 2.5 per day. There were three cases of upper respiratory infection, six cases of alimentary disturbances, i.e., three vomited, two developed colic and one had diarrhea. The distribution of alimentary upsets was not uniform but in the opposite sense of the group on whole milk formulae. There appeared somewhat more disturbances during the second and third month than during the first. Apparently dilution does not spare infants intestinal disturbances after the first month.

Series IV. Evaporated Milk Formula. Fifty-eight normal infants were maintained on an evaporated milk formula for three months. It consisted of evaporated milk, one to two dilution, with 10% added carbohydrate. The formula was started the second day of life in well newborns with a birth weight over six pounds. Although six of the group studied had difficult deliveries there were no post-natal manifestations. Orange juice and cod liver oil were introduced the third week. The orange juice was first given half strength and increased gradually so that two ounces were given by the end of the first month. The 10 D cod liver oil was offered five drops a day increasing it gradually until the infant received one teaspoonful a day. The formula was made up for twenty-four hours and divided into six feedings given at four hour intervals during the first month and subsequently into five feedings. The amount offered at each feeding was slightly above that usually taken by infants at each age level.

The average volume consumed per infant was 4.5 ounces per feeding during the first month, 5.0 during the second and 6.3 during the third month, the average volume for the total day's feeding being 25, 25, and 30 ounces respectively. The average caloric intake was about 66 calories per pound per day. The average gain in weight was 7.1 ounces per week and the average gain in height was one inch per month. The average number of stools was 2.6 per day. There were four cases of upper respiratory infection. Five developed alimentary disturbances, i.e., two vomited, one had colic, one diarrhea and one vomited associated with asthma.

Series V. Powdered Milk Formula. Sixty normal infants were maintained on a powdered milk formula for three months. It consisted of powdered milk, one tablespoonful to two ounces of water, with 10% added carbohydrate. The formula was started the second day of life in well newborns with a birth weight over six pounds. Although five of the group studied had difficult deliveries there were no post-natal manifestations. Orange juice and cod liver oil were introduced the third week. The orange juice was first given half strength and increased gradually so that two ounces were given by the end of the first month. The 10 D cod liver was offered five drops a day increasing it gradually until the infant received one teaspoonful a day. The formula was made up for twenty-four hours and divided into six feedings given at four hour intervals during the first month and subsequently into five feedings. The amount offered at each feeding was slightly above that usually taken by infants at each age level.

The average volume consumed per infant was 4.1 ounces per feeding during the first month, 5.1 during the second and 5.9 during the third month, the average volume for the total day's feeding being 24, 26, 29 ounces respectively. The average caloric intake was about 60 calories per pound per day. The average gain in weight was 6.4 ounces per week and the average gain in height was one inch per month. The average number of stools was 2.4 per day. There were five cases of upper respiratory infection including one with otitis media. Five developed alimentary disturbances, i.e., two vomited, one had colic, three developed diarrhea, one of which was secondary to an upper respiratory infection.

Series VI. Acid Milk Formula. Fifty-six normal infants were maintained on powdered lactic acid milk formula for three months. It consisted of one tablespoonful of the powder to two ounces of water, with 10% added carbohydrate. The formula was started the second day of life in well newborns with a birth weight over six pounds. Although seven of the group studied had difficult deliveries there were no post-natal manifestations. Orange juice and cod liver oil were introduced the third week. The orange juice was first given half strength and increased gradually so that two ounces were given by the end of the first month. The 10 D cod iver oil was offered five drops a day increasing it gradually until the infant received one teaspoonful a day. The formula was made up for twenty-four hours and divided into six feedings given at four hour intervals during the first month and subsequently into five feedings. The amount offered at each feeding was slightly above that usually taken by infants at each age level.

The average volume consumed by each infant was 3.8 ounces per feeding during the first month, 5.3 during the second and 6.2 during the third month, the average volume for the total day's feeding being 22, 26, 31 ounces per pound per day. The acid feedings were taken with more avidity after the first month. The average caloric intake was about 67 calories per pound per day. The average gain in weight was 7.1 ounces per week and the average gain in height was 1 inch per month. The average number of stools was 2.7 per day. There were three cases of upper respiratory infection. Five infants developed alimentary disturbances, i.e., one vomited, two had colic, two diarrhea and the feedings were reduced.

INDIVIDUALIZED FEEDING OF "STANDARD" FORMULAE IN WELL INFANTS

Every type of formula tested was effective routinely in over 80% of the infants studied. But in each group there were always a number of non-conformists. The particular formula was not adapted to them and they reacted with alimentary offense. Even mother's milk yielded its quota of digestive intolerance. The difficulty is with the infant in each group and not with any of the formulae tested. It appears improbable that any one type of feeding will ever be universally applicable to all infants.

The five series of routine formula feedings separ-

ated the normal infants from those with latent constitutional disorders. And even among the large group of normal infants in each series there were differences in the relative tolerance for milk as the first "solid" food. The range of digestive tolerance is so wide in most infants that no abnormal responses are manifest clinically with modified milk mixtures. But in infants with latent constitutional disorders — developmental, allergic, neuropathic — there is either a low digestive capacity for any food or a diminished tolerance for cow's milk, frequently below maintenance requirement. Not all these infants rebel against "standard" formulae because the infant's functional deviations may be slow in becoming manifest.

But the constitutional stigmata persists although not always poignantly. The routine feedings unsuited to these infants may tide them over the first months of difficult adjustment but subsequently contribute to the precipitation of their constitutional disease. What may develop will develop more violently if irritated by inappropriate feedings from birth. The feeding of routine formulae to well infants from birth ignores the prevalence of latent constitutional disturbances. Many of these can be recognized early and appropriate formula adapted to their more limited digestive capacities.

We attempted to distinguish normal from diathetic newborn to determine the type of milk indicated for each infant individually. Infants with overt disturbances were excluded from this study. Of the forty-five infants with diathesis, 65% were allergic, 30% neuropathic and 5% developmental in origin. The infants that developed allergic manifestations showed enough suggestion of latent allergy to warrant early adaptation of the formula. The most helpful sign was an erythematous linear fold in the post-auricular region or beneath the lobe of the ear, more striking beneath the left than the right ear. In addition the usual premonitory expressions of allergy such as a hairless scaly scalp and desquamated dry skin were helpful. When these manifestations in the newborn were corroborated by an allergic history in either parent the infant was considered a problem in latent allergy. Neuropathic infants were recognized by hypertonic manifestations during the first days of life. There was predominance of the flexor muscles with generalized and continued spasticity, restlessness, sleeplessness and irritability. Infants with latent developmental disorders were too varied to permit of any single procedure to be of value for early diagnosis.

Series VII. Individualized Formulae. Fifty normal infants were maintained on individualized formulae for three months. The type of feeding selected was in accordance with the indications of the individual infant. Long lean infants were given 75 calories per pound of body weight per day and lateral infants were given 60 calories. The former were fed concentrated whole milk mixtures, three to one dilution with 10% added carbohydrate, and the later diluted milk mixtures, one to one dilution with the same amount of added carbohydrate. Infants with latent allergy were given evaporated milk, one to two dilution with 10% added carbohydrate, with a caloric intake depending upon their body build. Infants with hypertonia were maintained on acid milk, one tablespoonful to two ounces of water with 10% added carbohydrate.

The formulae were started the second day of life in well newborns with a birth weight over six pounds. Although four of the group studied had difficult deliveries there were no post-natal manifestations. Orange juice and cod liver oil were introduced the third week. The orange juice was first given half strength and increased gradually so that two ounces were given by the end of the first month. The 10 D cod liver oil was offered five drops a day increasing

Milks indicated for infants

Infant Types (392 Babies)		
Linear (20%)	Medial (25%)	Lateral (55%)
Breast Milk	Breast Milk	Breast Milk
Cow's Milk (3:1)	Cow's Milk (2:1)	Cow's Milk (1:1)
Evaporated Milk (1:1)	Evaporated Milk (1:1½)	Evaporated Milk (1:2)
Powdered Milk (1:7)	Powdered Milk (1:8)	Powdered Milk (1:10)
Infant Diatheses (45 Cases)		
Allergic (65%)	Neuropathic (30%)	Developmental (5%)
Breast Milk	Breast Milk	Breast Milk
Goat's Milk	Thick Feeding	Evaporated Milk
Evaporated Milk	Evaporated Milk	Acid Milk
Powdered Milk	Acid Milk	
Vegetable Milk		

it gradually until the infant received one teaspoonful a day. The formulae were made up for twenty-four hours and divided into six feedings given at four hour intervals during the first month and subsequently into five feedings. The amount offered at each feeding was slightly above that usually taken by infants at each age level.

The average volume consumed per infant was 4.4 ounces per feeding during the first month, 5.5 during the second and 6.5 during the third month, the average volume for the total day's feedings being 26, 27 and 30 respectively. The average caloric intake was about 70 calories per pound per day. The average gain in weight was 7.3 ounces per week and the average gain in height one inch per month. The average number of stools was 2.6 per day. There were four cases of mild upper respiratory infection and one infant vomited.

EVALUATION OF RESULTS WITH ROUTINE AND INDIVIDUALIZED FEEDING

I. *Comparative Intake of Formulae.* The ingestion of various types of formulae was relatively uniform in amount for each group studied. During the first month the infants on breast milk took such varied amounts at each feeding that the average volume intake is of little significance in comparison with artificial feeding. Apparently the effort exerted in nursing is more of a factor than appetite in determining the volume intake at a feeding. The placid rôle of infants on artificial feeding accounts for the relatively uniform intake on the various types of prescribed formulae.

Infants took less of the acid formula during the first month but once they became adapted to it they took more of that formula than of the others. During the entire period of study infants took more of the processed milk formulae than of the whole milk formula. And those on individualized feedings consumed more per feeding as well as for the twenty-four hour cycle. This is partly due to the fact that more infants were

included in the series who have taken feedings steadily without alimentary upsets. The caloric intake per pound of body weight per twenty-four hours was greater on the more concentrated feedings, the least being with the diluted milk mixtures and the most with the acid and individualized formulae.

II. *Comparative Tolerance of Formulae.* Food tolerance is estimated clinically without quantitative criteria. It is difficult to make comparative estimates of the relative degrees of tolerance for the formulae tested. Quantitatively an infant's tolerance for a food represents the ratio of the maximum amount of the food he can metabolize without resultant disturbances by the maximum amount of that food metabolized by a normal infant of the same age group. We must necessarily deal with maximum rather than with optimum intake in the consideration of tolerance because we do not know what the optimum of any food is quantitatively for any infant. But we do know that there is a wide range between the minimum and the maximum and that any attempt to exceed the maximum produced a variety of disturbances essentially alimentary in nature. We are, therefore, led to the evaluation of tolerance of various formulae by a negative qualitative method of procedure. Those formulae consumed in the required amounts were considered well tolerated if they produced no untoward symptoms while those which produced digestive disturbances apparently exceeded the digestive capacities of the infants and were considered poorly tolerated.

All types of formula were well tolerated, excepting the whole milk mixture during the first month. There were the least number of digestive upsets on the individualized formulae and on the breast feeding throughout the feeding period studied. There were less digestive disturbances on breast feeding than on fresh milk formulae. Only significant symptoms of digestive disturbances were included in this evaluation of tolerance for much of the minor symptomatology was more an expression of mismanagement than of misfeeding. However, a feature that is frequently neglected in relation to food tolerance during the first three months of life is the increased nervous tone of infants in both breast and bottle feeding. It is usually alleviated by transient modification of the feeding quantitatively or qualitatively rather than by resorting to sedatives. The number and quality of the stools were not considered diagnostic of the normal range of alimentary function although frequency or abnormal character of stools were deemed pathognomonic of gastro-intestinal disturbance.

A striking feature of the two groups on the fresh milk mixtures was the relation between milk tolerance and body build in well infants. During the first two months there was a relatively great preponderance of digestive disturbances amongst those infants who were maintained on the whole milk formulae. Eighty per cent of those infants were of the lateral body build. Most of the linear type infants tolerated whole milk mixtures without any disturbances. Apart from food tolerance the caloric requirement from body surface considerations indicates that the linear infants require about seventy calories per pound of body weight while the lateral infants require about fifty-five calories. This difference in energy requirement appears to parallel their differences in tolerance. It is curious that the high gastric acidity during the first week of life should not increase the digestive capacities of all infants sufficiently to enable them to tolerate whole milk formulae. But after the second month the percentage of disturbances was parallel to those in the other groups.

A significant number of digestive upsets occurred in the group maintained on breast feeding. Excluding disturbances resulting from faulty technique in nursing those that persisted were of the same order of magnitude as in the infants on artificial feeding. The time-honored procedure of analyzing breast milk chemically for the gross constituents is considered irrelevant. Even analysis of the minutae is unnecessary because deficiency disease has a long latent period before inducing disturbances. The difficulty, we believe, is usually with the infant constitutionally and not with the milk chemically. But weaning was not deemed necessary until supplementary procedures failed to allay the disturbance.

The formulae prepared from processed milk were the best tolerated. Off hand, these would appear the most logical for routine use in infant feeding if nursing is impossible but such an approach defeats the very purpose of infant nutrition. The types of feeding that meets with the digestive capacities of the infants is indicated rather than that which least utilizes digestive mechanisms. It is the newborn's task to adapt to "foreign" foods—a biologic and therefore a physical necessity. Ability to digest a food is gained by ingesting the food in gradually increasing amounts. The more work the digestive mechanism is made to perform the greater the alimentary efficiency. The indications in normal infant feeding are fresh milk mixtures for the infants that can tolerate them and processed milk mixtures for those with diminished digestive capacities.

III. *Comparative Nutritional Status.* The adequacy of each type of feeding is best determined by the character and rate of growth of the infants of each group. But again growth evaluation is clinical rather than quantitative because we have no absolute standards of the composites of growth for each age level. Average weights and measurements of infants cannot be taken as guides for the developmental progress of an individual infant for the average infant is nonexistent. Developmental progress of an infant can best be evaluated in terms of himself as a standard and the increments of growth accruing at periodic intervals as the individual criteria of satisfactory achievement. These are based more upon clinical judgment than upon mere measurement. They include a variety of external manifestations of wellbeing such as type of facies, color of mucous membranes, condition of skin, quality of subcutaneous tissues, tissue turgor, muscle tone and skeletal characteristics. Even these properties of an infant are, during the first weeks of life, more an expression of his heredity and constitution than of the type of feeding instituted.

Each group of infants thrived on the various formulae as on the breast feeding. The greatest gain in weight was in those on individualized feeding and the least on the diluted milk formulae. The infants on breast feeding and on the processed milk formulae gained more rapidly than those on the fresh milk mixtures. The more concentrated the formulae the more rapid the weekly gain in weight. In no group did this necessarily represent mere accumulation of adipose

tissue. Despite the high gains in weight there were no manifestations of overfeeding. In fact we have observed no absolute relation between the high gains in weight and quantities of formulae ingested. This applies to both the breast and artificially fed infants. Large lateral infants, for example, with birth weights of about eight pounds made more satisfactory gains on twenty ounces of a formula per twenty-four hours than did the long lean infants with a birth weight of about seven pounds on an intake of twenty-five ounces. But on all types of feedings the gain in height was practically the same at least for the first three months. In each group the incidence of infection was about the same, acquired in most infants from adult contacts.

CONCLUSIONS

1. Comparative studies of "standard" formulae were made on 337 infants during the first three months of life with 55 breast fed infants as controls. The formulae consisted of whole milk, half diluted milk, evaporated milk (1 : 1), powdered whole milk (1 tablespoonful to 2 ounces of water), powdered lactic acid milk (1 tablespoonful to 2 ounces of water), each reinforced with 10% added carbohydrate. Each group maintained on a routine formula was compared with a group of 50 infants given individualized formulae.

2. The infants consumed more of the processed milk formulae than of the fresh milk formulae and the maximum was on individualized feedings throughout the period of study. The least number of digestive disturbances was observed on breast feeding and on individualized formulae.

3. The linear type infant required about 70 calories per pound of body weight and tolerated concentrated milk mixtures while the lateral type infant required about 55 calories per pound of body weight and tolerated diluted milk mixtures better.

4. Maximum gains in weight were observed in infants on individualized feeding and the minimum on diluted milk formulae. Infants on breast feedings and on processed milk feedings gained more rapidly than those on the fresh milk mixtures. The gains in height were the same on all types of feeding during the first three months. The incidence of infection was about the same for each group of infants studied.

5. Standard routine formulae were effective in over 80% of the infants studied. The residual nonconformists represented infants with latent constitutional disorders—organic, allergic and neuropathic—with either lowered digestive capacities or diminished tolerance. The early recognition of these types displaced routine by individualized feeding. This group showed the highest percentage of successful infant feeding.

A Case of Trichomonas Hominis Infestation

By

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KOFOID (1) points out the difference in the relative importance of the parasitic protozoa, such as the intestinal flagellates, and the hematozoa, *e.g.* trypanosomiasis, leishmaniasis, malaria, etc. The latter group is more catastrophic in its relations to the host than are the intestinal flagelloses. Kofoid believes that the flagellate parasites of the intestines may have more generalized capabilities of tissue invasion than has been hitherto suspected or detected. He states that there is abundant clinical evidence to the effect that they may be harmful when there is a disturbance of the normal bowel condition in the host due to exposure or infection as a result of which the resistance of the host is impaired.

Hinklemann (2) reports that 5 c.c. of blood from a human case of diarrhea and intermittent fever, mixed with distilled water and centrifuged, show all the features of Trichomonas intestinalis.

Ratz (3) found Trichomonas in the liver of pigeons.

The appearance of Trichomonas in pleural transudates and exudates in man as well as the cancers, ulcers, lesions of the mouth, jaw, tonsils, esophagus and stomach also occasionally in liver abscesses is suggestive that it may have tissue invasive powers.

The older German gastro-enterologists believed the flagellates to be non-pathogenic, occurring in the feces in most of the chronic diarrheas.

My experience has been limited to those more commonly occurring in my practice such as Trichomonas, Chilomastix mesnili, Giardia enterica, Cercomonas and Balantidium coli.

Close study of the feces of infected individuals give evidence of a low grade chronic entero-colitis. The treatment of all the flagellates that I have mentioned with *the exception of the Giardia enterica* is extremely simple. I employ stovarsol 0.25 gram tablet three times a day before meals for a period of three days. I have employed the follow-up method in a large number of cases and I have never known this drug to fail to completely destroy the organisms. The endamoeba coli is also quickly eradicated by this method of treatment.

There is no question about the pathogenicity of Giardia enterica. Quite a number of chronic duodenal ulcer patients show Giardia infestation. In my hands patients with Giardia infestation usually show a recurrence about four weeks after the treatment that was used.

Jelks (4) recommends transduodenal irrigations of a solution of neo-arsphenamine.

Barrow (5) and many others employ stovarsol or carbarsone.

Smithies (6) recommends five to ten grains of calomel followed by a saline. This dosage may be repeated in one week's time. The patient is given thymol

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after a "fat-free" diet and in obstinate cases small doses of neo-arsphenamine intravenously.

Recently I have employed a modification of the Smithies method. I give the large dose, grain 5 to 10, of calomel at bedtime followed in the morning by a mixture of magnesium and sodium sulphate. The following day 0.45 of neo-arsphenamine is given intravenously. The drug is injected very slowly and carefully to avoid any untoward sensitization which might occur in the patient. Two days later a second dose of 0.45 neo-arsphenamine is given. The follow-up of the ten patients whom I have treated show as yet no recurrence of the organisms. The *rationale* of this method of treatment is probably the large dose of intravenous arsphenamine administered while protozoa are weakened by the calomel and saline.

CASE REPORT

Recently I came across a very unusual case of infestation by Trichimonas hominis:

Male, white, aged 52. Salesmanager. Height 6 foot, 1 inch. Weight 255 pounds. Came under Dr. Hanford Phillips care August 17, 1936. His chief complaint was dull pain in the sacro-iliac and lower lumbar region. One week ago he had had prostatic massage and a urethral sound was passed which was followed by chill and high fever. He developed what appeared to be an acute cystitis. Staphylococcus was grown on the culture. Within a few days he developed an eruption of purpura hemorrhagica involving the lower extremities and forearms. Finally on September 8, he had an attack of severe pain in the upper abdomen with vomiting and fever. He was sent to the Missouri Baptist Hospital on September 11. Blood analysis as follows: Red blood cells 4,750,000, Leucocytes 20,800. Differential: Eosinophiles 1, Stabkernige 24, Segmented 53, Lymphocytes 17, Monocytes 5, Blood playelet count—290,000. Stool culture was negative for typhoid and the Bargen diplococcus.

He continued to have fever and needed sedatives for the pain. The feces analysis on September 14 showed strong positive occult blood reaction.

X-ray examination by Dr. Arthur C. Echternacht revealed the following findings: "Fluoroscopic examination of the chest preceding the ingestion of an opaque meal reveals no gross pathological changes. The stomach, which was of the "steer-horn" type, filled readily and a normal gastric tone and peristalsis was observed. There was no evidence of an intrinsic gastric or duodenal lesion. Three hour film shows only a trace of barium remaining in the stomach. The head of the barium meal had reached the cecum. There was a large quantity of barium remaining in the upper portion of the small intestinal tract which shows the calibre to be unusually large, also the outline of the lumen of the small bowel crossing the spine which suggests the possibility of a neoplasm. However, that may be due to intrinsic pressure. The six hour film shows the stomach to be completely empty of the barium meal with a large portion of the meal remaining in the upper portion of the small intestinal tract at approximately the same location as was seen on the three hour film. This portion of the small bowel still shows an unusual dilatation also an irregularity of the small bowel as it crosses the spine as was seen on the three hour film. The retention of the barium in the same location of the small bowel suggests the possibility of some obstruction distal to this point. The head of the barium column had reached the hepatic flexure of the colon. Twenty-four hour fluoroscopic examination reveals the barium to be in the cecum, ascending, and transverse colon, also sigmoid and rectum. Fluoroscopic study of the colon during the administration of a barium enema reveals the shadow casting solution to pass readily through the colon from the rectum to the cecum.

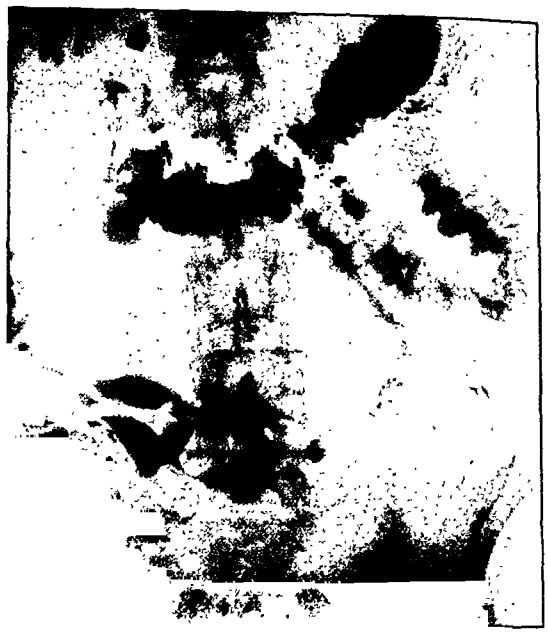


Fig. 1. Three hour film. Stomach empty. Dilatation of the duodenum and jejunum and irregularity of the jejunum at its junction with the ileum. N.B. The 6 hour film was almost identical with this one.

There were no irregularities noted anywhere along the colon. Conclusions—G. I. X-ray examination suggests the possibility of a partial obstruction in the upper portion of the small intestinal tract, possibly from two to four feet from the pylorus." I present one of the films. (Fig. 1).

On September 22, I was called in consultation with Drs. Hanford Phillips and John W. Hotz, and from a study of the history and review of the X-ray findings and the strong occult blood reaction in the feces, made a diagnosis of carcinoma involving the jejunum, and advised surgery. Dr. Hotz operated on September 24. His findings are as follows: "Left para-median incision-muscle retracted laterally. Abdomen opened—no free fluid. Liver was not enlarged, edges were free and smooth. Gall bladder soft and emptied freely. Foramen of Winslow showed nothing. Stomach was soft and had no abnormalities. Pancreas was smooth, normal consistency, not enlarged. Both kidneys were normal. Spleen was small, edges smooth. Colon is smooth, no masses, somewhat distended to palpation. Exploration of the small bowel reveals that from the ligament of Treitz extending down throughout the entire angle of the jejunum, the bowel was distended, thick, having a soft doughy consistency, about four times as large as the ileum. The mesentery was normal, however the entire jejunum was covered with minute blood vessels which bled into the wall of the bowel on the slightest provocation."

The question arose as to whether the condition of the jejunum was a manifestation of purpura or the staphylococcus infection in the bladder. The bladder condition readily cleared up after a course of large doses of sodium benzoate.

At this time I secured a specimen of the feces and found it to contain a large number of Trichomonas hominis. I at once administered the specific medication of stovarsol for a period of three days. Improvement was now rapid. Temperature subsided. He was able to retain his food and the occult blood disappeared from the feces. The purpura completely disappeared from the skin. X-ray films of the spine revealed the presence of an exudative arthritis involving the lumbar and sacro-iliac joints.

He was able to return to his home two weeks after the operation. He was now put on a low cholesterol diet, given two grains of dessicated thyroid once daily and twenty drops of saturated solution of sodium iodide three times a day. Both of these drugs are lipoid solvents. A sacroiliac and lumbar spine belt was prescribed.

He has made splendid response to treatment. His weight is now 220 pounds. He is active in his work, his general condition is splendid, feces are now normal in appearance and free from mucus.

In my opinion, the acute process found in the jejunum was produced by the Trichomonas hominis because it rapidly subsided after the administration of the specific drug—*stovarsol.*

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Colitis Ulcerosas Graves No Amibianas Etiologia, Diagnostica Y Tratamiento Medico

By

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ULCERATIVE colitis is a disease of the large bowel which has been called "idiopathic" by the old authors and "gravis" by the Germans; some authors, particularly the Americans, recently have called it "bacterial."

The disease is characterized by a series of well-defined symptoms, a typical proctoscopic picture, a tendency to recur, and a bad prognosis. The anatomopathologic changes consist of inflammation and diffuse erosion of the large intestine; the evolution is purely destructive. The small bowel is usually not involved. The large bowel may be totally or only partially involved. A sharp demarcation between the pathologic and the healthy segments of intestine practically never exists. Microscopically, the disease is conspicious by the presence of numerous ulcers in the colon. The appearance of these ulcers is variable in different portions of the colon.

In some regions of the colon the ulcers are of different diameter but are small and numerous. Histologically, the mucosa in the borders of the ulcers disappears suddenly and does not show any defensive reaction. The most intense destructive reaction is found in the submucosa; the loss of the mucosa seems to depend on a primary modification in the submucosa. The destructive process has a dissecting tendency; it slowly destroys the vascular connective tissue of the submucosa. The mucosa resists and is saved; the connective tissue of the submucosa dies because of lack of nutrition as a result of the destruction of the blood vessels. The walls of the ulcers do not show any sclerosing phenomena. The only reaction is a perivascular infiltration with lymphocytes, plasmocytes and histiocytes. Sometimes, the ulcerated regions of the colon are larger than the regions covered by mucosa. The muscle may be exposed and in some places one may see islands or strips of mucosa, which sometimes form polypoid elevations. In the sigmoid flexure and rectum, one sometimes sees extensive ulcers whose longest axes are directed longitudinally. These ulcers are different from the ones previously described, because they are not so deep and the mucosa around them is congested and bleeds easily. Histologically, the only difference is that in the ulcers in the sigmoid flexure and rectum there is greater congestion in the vessels of the submucosa and there is a more abundant exudate between the necrotic tissues of the ulcers. The necrotic tissues have a fibrinous appearance. Sometimes, the destructive process extends through the muscular layer and perforation kills the patient. The tissues around the perforation are greenish. When the muscular destruction is produced in the lower portion of the rectum (extraperitoneal) the result is an infection of the perirectal tissues and the formation of an abscess.

ETIOLOGY

The authors reviewed the etiology of ulcerative colitis. They said that the bacterium which was found by Bargen is a diplostreptococcus which is easily isolated by Rosenow's method. In fact, if one makes cultures from the intestinal ulcers, in Rosenow's fluid brain medium, and if one maintains them under conditions of proper oxygen tension or anaerobically and follows the steps advised by Bargen, and makes subcultures on agar-blood plates or makes cultures from the mesenteric lymph nodes of rabbits which previously have received inoculations, it is very rarely

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that one does not find bacteria that have the cultural characteristics of the diplostreptococcus.

Happily, the Bargen technic for identification of the diplostreptococcus is simple. Bargen said the diplostreptococcus has hemolytic properties and that the hemoglobin becomes green. It seemed that the diplostreptococcus of Bargen, according to the classification of Brown, should be considered as a streptococcus mitis, variety, number 2. The streptococcus mitis is a well known bacterium that is found in many infectious processes. It frequently is found in the mucosa of the upper part of the respiratory tract of healthy persons or of patients who have subacute or chronic inflammations. To give this organism etiologic significance it is necessary to take into account the theory of elective localization propounded by Rosenow and others.

The authors studied bacteriologically twenty-five characteristic cases of ulcerative colitis and twenty-five cases which were used as controls. They found the Streptococcus mitis in 30 per cent of the cases of chronic ulcerative colitis and also in 25 per cent of the cases which were used as controls. The Streptococcus saprophyticus, which has been described by Buttiaux and Sevin as the cause of certain types of ulcerative colitis, was present in 8 per cent of the cases of chronic ulcerative colitis and in 16 per cent of the cases which served as controls. In one case the diplostreptococcus which was isolated was of the infrequent type, which is very different from the type described by Bargen. In this case the diplostreptococcus was isolated from rectal ulcers and from ulcers that later developed on the skin and mucous membrane. The ulcers of the skin and mucous membrane were very much like the ones in the rectum. The authors expressed the opinion that different kinds of streptococci can have a pathogenic action in certain phases of chronic ulcerative colitis.

The authors did a good deal of experimental work. They injected, intravenously, large numbers of bacteria into rabbits and dogs. Characteristic lesions occurred only rarely. The authors said that among the different bacteria that have been considered the cause of ulcerative colitis, streptococci are most important. When one makes bacteriologic examinations of specimens obtained from intestinal lesions, one's attention is called to the small number of bacteria found. The cultures obtained from scrapings of diseased mucosa which are made in Rosenow's medium and the subcultures which are made in the same medium always permit the isolation of a diplostreptococcus or short chains that initially have the characteristics that Bargen attributed to his diplostreptococcus of ulcerative colitis. This bacterium and most of the diplostreptococci found in ulcerative colitis often have a pathogenic action when injected into rabbits. The same bacteria isolated from healthy people usually have no pathogenic action.

The authors investigated the part the filtrable virus played in the production of chronic ulcerative colitis. They took scrapings of the intestinal mucosa of healthy persons and of the ulcers of chronic ulcerative colitis. Afterward, they made an emulsion in sterile physiologic saline solution and filtered it through a filter L.3 and injected that filtrate into the brains (0.2 c.c.) and veins (3 c.c.) of rabbits. The lesions produced by the injection of the filtrate were remarkable, and sometimes were situated in the intestine. These lesions were comparable to those produced by injection of pure cultures of the streptococci. Lesions did not develop in the animals which were used as controls. This fact suggested to them that in ulcerative colitis there exists some principle which confers pathogenic value to bacteria that ordinarily are not pathogenic.

The authors made further experiments trying to determine whether chronic ulcerative colitis was produced by a filtrable virus. They observed that the virus lost its action when cultivated in solid medium and after subcultures had been made; furthermore, they observed that when it was cultivated in the fluid medium of Rosenow, it was much more active, especially after the first transfer, but its action was complex. It produced more acute lesions because it was associated with other toxic substances which were derived from the bacteria. The virus is maintained at the expense of the live streptococci, when these are cultivated in anaerobic conditions and mainly in fluid medium. For these reasons the authors used to make injections of direct filtrates. The virus, they said, can be isolated from patients who have acute, subacute, or chronic ulcerative colitis. However, they thought that it had more pathogenic power or that it occurred in larger amounts when it was obtained from patients who had acute ulcerative colitis. In order to obtain an emulsion of the virus the patient was given an enema of 1000 c.c. of physiologic saline solution. The mucosa was cleansed with the aid of a proctoscope and the ulcers then were scraped four or five times and the material placed in 20 c.c. of sterile physiologic saline solution. The tube was shaken energetically and the emulsion was filtered through sterile filter paper. After this first filtration, the filtrate was filtered through a new, sterile, dry, porcelain filter (L.3). The filtrate was kept in an icebox at a temperature between 1° and 5° C.

After the virus was injected into animals, it was distributed throughout the body, especially in the spleen, and it always could be isolated again by maceration of one part of spleen in 10 parts of physiologic saline solution.

The virus may be administered to animals subcutaneously, intravenously, or intracerebrally. The results of the experimental disease were about the same regardless of the method of administration; however, the authors preferred the intravenous method. If the animal was a rabbit, 3 c.c. of the virus per kg. of body weight was given; if it was a guinea-pig, 1 c.c. per kg. of body weight was given, and if it was a dog, 0.5 c.c. per kg. of body weight was given. The animals which were most sensitive to the virus were the dog and rabbit; the sensitiveness of these animals was very similar. The guinea-pig was only slightly sensitive and the rat was not sensitive at all.

The authors considered the virus isolated only when they could produce the disease in a series of animals. Many animals died from intercurrent diseases. Successive passages through animals had a tendency to decrease the activity of the virus. After the virus had been passed through four or five animals, it lost its virulence, although it occasionally retained its virulence after passage through nine or ten animals. The passage from one animal to another of a different species also decreased the virulence of the virus.

It was impossible to isolate the virus in all stages

of chronic ulcerative colitis, and all of the rabbits which received injections of the virus did not become ill. Local lesions did not occur at the point of injection. Fifty-five per cent of the rabbits which received injections of filtrates became ill, and 88 per cent of those which received injections of filtrates that had been passed once through Rosenow's culture medium became ill. Of the rabbits which received injections of a virus that previously had been passed through another rabbit, 40 per cent became ill, and 33 per cent of those which received injections of a virus that previously had been passed through two rabbits became ill. After that the percentage did not decrease in the same order; on the contrary, when the virus had been passed through several animals of the same species, its virulence increased again and 70 to 80 per cent of the animals that received subsequent injections of the virus became ill. Almost all the rabbits had diarrhea and some of them passed bloody stools. They became weaker and weaker until they died.

In the digestive tract of the animals were found lesions which varied from simple congestion to deep ulceration; however, the most frequent lesions were small hemorrhages in the mucosa and submucosa. These lesions were particularly frequent in the rectum and small intestine. When animals lived more than one month, these lesions produced stenosis. Hemorrhagic and desquamative changes were occasionally seen in the stomach, liver, kidneys, suprarenal glands and nervous system. About 50 per cent of the rabbits that received injections of the virus died within ten days, and 10 per cent died between twenty and forty days after the injection.

The experimental disease of dogs was more like the chronic ulcerative colitis of man than it was of rabbits. A few days after the injection, the dogs began to show evidence of intestinal disturbances. These were ushered in by diarrhea; the stools usually contained a large amount of blood. The animals did not eat and they became more and more cachectic until they died. Some of the dogs seemed to overcome the disease, but ten or twelve days later they had a recurrence. At this time the stools usually were more profuse and contained more blood than they had at the onset. In some cases a localization in a vital organ killed the animals quickly. Often, the organs of vision were affected; this produced blindness which was total or partial and permanent or transitional. Examination of the digestive tract revealed lesions which extended from the stomach to the rectum; inflammatory regions alternated with other regions in which the mucosa appeared normal. The lymph follicles of the mucosa were enlarged and filled with bloody material. More than 80 per cent of the dogs that received injections of a virus obtained from patients who had an acute phase of chronic ulcerative colitis became ill.

The authors expressed the opinion that the resulting lesions initially originated in the blood vessels. Furthermore, they were of the opinion that the virus produced vascular lesions. The small vessels of the intestine were readily damaged. The primary reactions against the virus were probably produced by the reticulo-endothelial system, mainly by the endothelial cells of the vessels, which finally produced emboli. Then the vessels without endothelium permitted the blood to pass through into the connective tissue and peri-endothelial tissue. These hemorrhages compressed the vessels and produced obliteration. Damage to the walls of the vessels and obliteration of the vessels were the fundamental factors from which were derived all the anatomopathologic features of the experimental disease. When the lesions affected mainly the intestinal villi, there were congestion and edema of the mucosa, desquamation of the epithelium, and small hemorrhages. All these alterations in the vessels and the secondary modification that followed made the intestinal mucosa a good field for implantation of other bacteria, which frequently changed the anatomopathologic picture. The Streptococcus mitis mainly, and other species of streptococci, and several kinds of bacteria found in the lesions made conditions ideal for the development of chronic ulcerative colitis. The virus was not different in its pathogenic action from the virus of scarlatina. Like the latter virus, it produces among human beings a disease in which it is difficult to separate the action of the virus from the action of the bacteria which play an important but secondary part.

CLINICAL OBSERVATIONS

The authors expressed the opinion that the ulcers seen in the digestive tracts of patients were the result of simple secondary infection produced mainly by the Streptococcus mitis. This opinion was based on the observation of ten patients who had chronic ulcerative colitis and twenty human beings who served as controls.

In more than three-fourths of the cases the patients had a little fever, and in some acute forms of the disease the temperature reached 104° F. and occasionally it was maintained for more than two months. Sometimes, the fever was of a septic character without any apparent complication. One of the more constant symptoms observed was a slight anemia. It was marked in some acute forms and in certain chronic forms in which the preponderant symptom was bleeding. A slight leukocytosis usually was noted and there was a deviation of the leukocytes to the left but the authors never noted an increase in eosinophils, as described by Albu. The authors emphasized the value of proctoscopic examination, and said that one never can say that a patient is cured if the rectosigmoidoscopy and the roentgenograms do not prove it. Four of their patients who had acute ulcerative colitis died in less than four months, and one died in a few weeks. Some were cured, but in other cases the disease became chronic. In most of the cases of chronic ulcerative colitis the disease was chronic from the beginning and was characterized by recurrences, alternating with phases without symptoms.

The authors divided the complications of chronic ulcerative colitis into local, or intracolic, and extracolic. They referred to the former as the most frequent and reported that they comprised polyposis of the rectosigmoid, diffuse polyposis throughout all the colon, rectal stenosis, stenosis of the sigmoid colon, neoplastic degeneration, and perforation. They never noted a fatal hemorrhage in the cases which they observed.

Extracolic complications included arthritis of the wrists, shoulders, and tibiotarsal joints; perirectal abscess and multiple fistulas; nephritis; ulcerations of the skin and palate; purpura and phlebitis. In one case of acute ulcerative colitis the authors noted

splenomegaly which disappeared when the disease became chronic, and reappeared during a recurrence. In one other case the patient also had perirectal abscess, ulceration of the palate, arthritis, pseudotuberculides of the skin, and pyodermitis. Another patient had chronic ulcerative colitis, polyposis, and cancer.

Most of the patients who had perirectal abscesses were cured only by ileostomy or colostomy. Arthritis was a frequent complication, particularly in acute stages, and the authors noted that arthritis tended to occur with each recurrence. However, arthritis was usually chronic and did not respond to the administration of salicylates.

TREATMENT

The authors were skeptical of the results of treatment. Results with irrigations have been very discouraging. Mechanical cleansing with physiologic saline solution seems helpful. They reviewed the different treatments proposed. Mediocre results followed the administration of Bargen's serum and vaccines. They did not see any local improvement as a result of Rachwalsky's treatment with blood transfusions. They tried Logan's treatment, which consists of the administration of tincture of iodine, the autohemotherapy proposed by Bensaude, the administration of calcium and parathyroid extract advised by Haskell, and the Kalk treatment. The best results were obtained with the administration of reduced iron (2 to 4 gm. a day) and with the administration of opium for a long time.

They advised an adequate diet which was high in calories and vitamins, low in residue (cellulose), and easily digestible. They allowed some light alcoholic drinks with the meals.

COMMENT BY ABSTRACTORS

The results of treatment reported in this monograph differ from those obtained by the abstractors. Our experimental work would suggest that the essential lesions may be caused by the streptococcus or its toxins. The work of the authors of this monograph indicates that the damage is done by the filtrable virus in association with the streptococcus.

Causes and Treatment of Peptic Ulcer*

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BY the term "peptic ulcer" we refer, in this paper, to gastric or duodenal ulcer produced by the corrosive action of the acid chyme on the mucous membrane. This definition excludes ulcers resulting from arteriosclerosis, specific infections or malignant growths.

The Causes of Peptic Ulcer: Various opinions and hypotheses have been advanced as to the causes of this condition (1, 2) and a great deal of confusion prevails because one writer describes as essential factors which other authors consider purely secondary.

The subject would be made much clearer and easier to grasp, if we could classify the causes of ulcer in a simple and rational manner.

Aristotle, in his "Logic" laid down the different kinds of causes, namely: the *material,* the *formal,* the *efficient,* and the *final.* To these, various old church writers added the *occasional cause.* As really important causes, for example, in the construction of a house, we have:

I. The material (stone, marble, wood) of which the house is made—this is the *material cause.*

II. Some special event or circumstance, such as marriage, an increase of family, etc., to be commemorated—this is the *occasional cause.*

III. The plan, type or pattern of the architect giving the location, size, shape and architecture of the building—this is the *formal cause.*

IV. The energy of the workmen who actually build the place—this is the *efficient cause.*

V. The will or final motive of the owner who decides and gives the order to build—this is the *final cause.*

Modern metaphysicians have discarded this classification as being too simple and inadequate when applied to spiritual conceptions. We physicians, being chiefly concerned with terrestrial things, find that it still retains its value in helping us to distinguish physical causes so that we may have a clear idea of what we are doing and of what we are talking about.

If we examine the causes of peptic ulcer in the light of the foregoing classifications, we find the following:

I. THE MATERIAL CAUSE

This lies in the biological structure of the tissue—the gastric and duodenal mucosa—in which the ulcer originates.

Ochsner (3) and others assume that, in certain persons, there is an inherent susceptibility of the tissues, a lack of resistance to the action of the gastric chyme. What is this material defect in the mucous membrane that makes it more vulnerable in some people than in others? We do not know. This being, however, the soil on which the ulcer grows, attempts have been made to modify its composition by using subcutaneous, intravenous or intramuscular injections of various substances such as pepsine, sodium benzoate, nonspecific proteins, milk, etc., with the idea of improving the chemical structure and the resistance of the mucosa.

In 1933, Aron and Weiss (4), experimenting on dogs, found that the loss of amino-acids, by weakening the tissues, caused ulcers to appear in the stomach and in the jejunum; these ulcers, they believed, were cured

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or prevented by the subcutaneous injection of histidine. The Hoffmann-LaRoche firm immediately put on the market their product "Larostidine" which many people are trying at the present time.

The hypothesis advanced by Aron and Weiss fails to explain why so many people who are on a regular diet, including amino-acids, should develop ulcers. The symptomatic cures obtained by this method are mostly of the "objective" kind. Some observers are very enthusiastic; others remain skeptical about it. It will take years before the final results of this therapy can be determined, especially as regards recurrence.

Though it is interesting to see the problem attacked from the somewhat neglected angle of the "material cause," we shall have to admit with Ochsner that, for the present, the susceptibility of tissue is still an uncontrollable factor.

II. THE OCCASIONAL CAUSE

The occasional cause is represented first by small injuries to the gastric mucous membrane resulting from various agents which are either *mechanical*, such as abrasions by foreign bodies, roughage, and operative wounds, or *chemical*, for example, erosions caused by acid foods, stimulants, spices, tobacco and other irritants; secondly, by circulatory disturbances such as local anemia (anemic spots of Aschoff) (5) with vascular spasm; or congestion (small hemorrhagic spots of Virchow) (6) followed by small patches of necrosis. These changes may be caused by *physical agents* (very hot or very cold drinks), local inflammation, or distant foci of infection such as infected tonsils or apical abscess producing small bacterial emboli, the action of toxins (burns, uremia); common colds, general infections, emboli after abdominal operations, etc.

It is not probable that any of the foregoing occurrences could start an ulcer in the absence of hyperacidity which always remains the condition *sine qua non*. Aschoff (5) showed in animal experiments that purely mechanical lesions heal very quickly. The majority of these small patches of toxic-infectious necrosis heal readily when general infection subsides and when the toxemia is not too great. This is proved by the great number of scars found in the gastro-duodenum at necropsy (in 10 per cent of all cadavers, according to Hurst and Stewart (7).

The occasional causes are not essential; the gastric juice, if strong enough at a certain point, can probably start an ulcer without extraneous help. Nevertheless, if abnormal acidity prevails, the occasional causes will favor ulceration and will mark its beginning, thereby becoming contributory factors of considerable importance. (Indeed, it is an open question whether the lesions caused by roughage, abuse of spices and stimulants, etc., when constantly repeated, may not set up a local inflammation of the mucosa and a chronic irritation of the gastric nerves, so as to bring about, by reflex, an increase of the acid secretion. This, in turn, would produce an ulcer. We shall discuss this point under "final" causes). As we do not know which patients are hyperacid, or will become so in the course of time, it is always better to prevent or to correct the action of the occasional causes by proper diet, by removal of foci of infection, by gentle technic at operation, avoiding mass ligatures of the omentum, etc.

III. THE FORMAL CAUSE

We do not attach much importance to the form or appearance of individual peptic ulcers; they are essentially the same as those of ulcers in various other regions of the body.

The distinctive feature of the peptic ulcer lies in its localization along the lesser curvature (the gastric pathway of Aschoff) (5), and on either side (gastric and duodenal) of the pylorus. The distribution and extent of the process are determined by the peculiar shape of the stomach and the mechanism of the pyloric sphincter. Nature made the antrum like a funnel tapering toward a narrow orifice, the pyloric strait, which opens and closes intermittently, in order to maintain a proper titre of hydrochloric acid during the function of digestion. According to physiologists (8) we have here *a self-regulating mechanism* by which the freshly secreted gastric juice of 0.5 per cent strength is brought down to an acidity from 0.15 to 0.2 per cent in strength by regurgitation of the pancreatic juice into the stomach—at least such is the case in healthy subjects.

In disease, however, the situation becomes quite different: if the pylorus fails to open properly, the titre of the gastric chyme remains too high and the strong acid will burn a hole in the mucosa of the stomach or in the wall of the duodenum when suddenly projected into it. This special conformation of the antrum and of the pylorus is the factor that localizes the ulcer along the lesser curvature and on one side or the other of the sphincter: as such we consider it the *formal cause* of the ulcer.

Many special methods have been devised to correct this condition, all with the same object in view, namely to circumvent or to suppress the pyloric "strait" so as to neutralize the action of the gastric chyme by an increased regurgitation of the duodenal contents into the stomach. The main types of operations recommended as gastroduodenostomy, gastrojejunostomy and partial gastrectomy.

It is not the purpose of this paper to enter into the question of surgical technic in this connection. Each type of operation, as well as each modification of the various technics employed, has its adherents. In any event, the indications for gastric surgery must be established with very great caution and with due consideration of the many factors which must influence a decision, for example: deformity of the stomach, the intractability of the ulcer, the possibility of malignant degeneration, hemorrhage, perforation, the age of the patient, his general condition, and so forth.

Surgical intervention, so often thought of as "radical" is, in reality, very largely palliative. It is directed toward the formal cause of ulcer, namely the peculiar shape of the antrum or the pylorus, and its object is to prevent the formation of a pool of strong acid in the antrum. In achieving this, it partially neutralizes the gastric chyme *after* it has been secreted and so, indirectly, it acts also against the efficient cause, that is, the secretory power of the stomach. Operation, however, does not strike at the source of the acid production, nor does it attack the final cause of the disease. This is the weak point in gastric surgery, and this is the reason it is not always suc-

cessful. Medical treatment, therefore, remains the basis of all our therapy, and operation should be considered only as an adjuvant to internal medicine.

IV. THE EFFICIENT CAUSE

As such we consider the nervous energy, especially the neurosecretory mechanism governing and regulating the output of hydrochloric acid, which itself is only an agent and a part of the efficient cause. It is the disturbance of this mechanism which actually produces the peptic ulcer.

As component parts of this apparatus we have: the gastric glands and muscle fibers, the plexuses of Meissner and Auerbach, the sympathetic ganglia and trunks with the rami communicantes, the spinal cord, and finally the central nervous system, which has also, through the nervi vagi (X) another more direct connection with the stomach.

The gastric juice or chyme is produced during the process of digestion, (the total amount being 1 or 2 liters a day): at the same time peristaltic waves, moving at the rate of about 3 a minute, mix the acid with the food; the pylorus, acting as a regulator (8), opens from time to time and allows some regurgitation of the pancreatic juice into the stomach. Then (and this is also an important function of the nervous mechanism) when digestion is completed the supply of hydrochloric acid is shut off so that normally none should be found in the empty stomach.

The activity of the nervous parts is influenced by various factors, such as local irritants, peritoneal inflammation, central (psychic) stimuli, hormones, alkaloids, etc. (9, 10, 11).

From all the experiments that have been made and all the opinions that have been advanced, we are inclined to believe that there are two distinct portions of the nervous system involved in the function of digestion.

1. The "vegetative-reflex" portion, consisting of the peripheral nerves and spinal arcs, with the interposition of the sympathetic chain acting as a sort of shock-absorber in both directions, the whole being connected with the brain by tracts of the spinal cord, but working with a certain degree of autonomy.

2. The central portion (cerebral centers and vagus nerves) which normally has only a small participation in the process of digestion, though on certain occasions, the psychic stimuli enter into play and are transmitted to the stomach by the tenth nerve. If the action of the vagus is deficient (depression, apathy) there may be atony of the stomach; if it is excessive (fright, excitement, over stimulation) there is increased peristalsis, spasm, hypersecretion, even pyloric closure with vomiting, etc.

The Neurogenic Theory of Peptic Ulcer: Rokitanskey (cited by Cushing (10) was the first to teach that certain peptic ulcers are caused by *"a diseased innervation of the stomach, owing to a morbid condition of the vagus causing extreme acidification of the gastric juice."* This point was brilliantly demonstrated by Cushing in a series of cases of brain tumor complicated by gastric ulcer, some of them with perforation. In the overwhelming majority of cases the alteration in the nervous center is only functional (excessive stimulation) but nevertheless its effects are severe and the theory of the neurogenic origin of peptic ulcer has gained ground steadily. Eppinger and Hess (12) supported it by their studies of vagotonia. Von Bergmann (11, 15) and his pupils did much to foster this theory. They also called attention to the anemic patches with consequent ulceration caused by occlusion of the vessels as a result of intense muscle spasms. Hurst and Stewart (7) also speak of a "hypersthenic" gastric diathesis.

Theoretically, the nervous disturbance may originate either in the peripheral vegetative reflex part or in the central part of the nervous system. (We shall return to this point under the discussion of the final cause). As a rule, however, we may say that the vegetative reflex system behaves like an honest laborer doing his work in a humble, unspectacular, orderly manner, while the central nervous system may be likened to a labor agitator intent on sabotage and constantly striving to drag the other fellow away from the regular performance of his duty. By interfering with the quiet, automatic, clock-like process of digestion, the central nervous system acts as a troublemaker and a disturber of the peace.

PATHOLOGY

Secretion: The essential factor in the formation of ulcer is a change in the secretion of hydrochloric acid by the stomach. We call it "hyperacidity" which may not be quite accurate. Von Bergmann (13) investigated the exact titre of acidity in a large series of patients and found the following:

	Gastric ulcer	Duodenal ulcer
Hypoacidity (anacidity)	35%	0%
Normal acidity	41%	57%
Hyperacidity	24%	43%

These findings indicate that only a minority of patients with peptic ulcer have actual hyperacidity. The serious aspect of the change in secretion lies not so much in the amount of acid formed as in the time of secretion and the fact that acid is found in the empty stomach, especially at night. It is the *bad timing* of the acid production, a dysfunction of the neurosecretory mechanism, which constitutes the outstanding phenomenon of ulcer. The nervous system may be compared to a careless watchman who is supposed to control a certain faucet but fails to do so; in the case of gastric ulcer, the "watchman" opens the faucet of secretion too early, before there is enough food in the stomach to neutralize the hydrochloric acid which pours into it; the consequence is pain as soon as the patient begins his meal, though he usually is fairly comfortable between and before meals. In the case of a duodenal ulcer, the "watchman" forgets to close the faucet tightly after digestion is complete, acid keeps trickling down the walls of the stomach causing much spasm and pain which the patient feels four, five, six or more hours after meals. It is most troublesome at night, usually waking the patient at 1:00 or 2:00 a.m. Ingestion of food relieves the pain. It seems that food absorbs the hydrochloric acid like a sponge and so protects the mucosa, but if acid is secreted between meals there will be pain and danger of ulceration. Bockus (14) found this "postprandial" acidity in 84 per cent of the patients with duodenal ulcer.

Sensation and Motility: The first effect of the presence of hydrochloric acid in an empty stomach is to cause pain of spasmodic nature (15), and this is rarely absent. In acute ulcers or in acute exacerba-

tions of chronic ulcers there are often periods of severe, even intense, pain lasting for weeks or months. We may call these periods *acid crises*. The secretory power of the nervous system pours hydrochloric acid into the stomach in large quantities and to this stimulus the muscles — especially the pylorus — react constantly with painful spasms. Once started, an ulcer will also, by reflex, cause more spasm and more secretion. This results in deeper ulceration, and such a vicious circle becomes established that it is impossible to say what was primary, the whole gastric mucosa being in such a state of erethism that even the blandest foods cause irritation and pain.

Treatment of the Efficient Cause: Our chief weapon against this factor has been insistence on a strict diet, with alkaline medication, in order to limit the production of acid and to have it properly timed, thereby protecting the autonomous process of digestion.

Though such provocative agents as stimulants and spices are known to cause much acidity and pain in patients with ulcer, the worst offenders seem to be the animal proteins. Yet it is difficult to do without them, as most people who are active are not satisfied with a purely vegetarian diet.

I have found that a good plan is to give the patient whatever red meat (liver, kidney, boiled beef, etc.) he is allowed to have, at his breakfast; during the morning he may carry some chalk tablets with him and eat them in case of pain. He should have a lunch low in protein, with fish or cream cheese or two eggs at the most. Then, and this is the important point — the evening meal should contain no animal protein of any kind, not even cream cheese, eggs, milk, broth or ovaltine. It should consist only of pureed vegetables or fruit and some cereal or paste. A meal of this kind will "mop up" whatever acid has oozed down the wall of the stomach after the previous digestion, but will not start the secretion of new acid in excess, and this is, in my experience, the most efficient single measure by which the patient may regain his much needed sleep.

This medical treatment, though usually successful, is not uniformly so because it does not correct the final causes of the trouble.

For some reason difficult to understand, most of the advocates of the neurogenic theory have failed to draw the full conclusions from their premises. If gastric secretion is under the control of the nervous system, and if a peptic ulcer is a manifestation of a derangement of that system, it follows logically that, in order to cure this condition, we should make our frontal attack against the factors injuring the nerves, i.e., against the *final causes*.

V. THE FINAL CAUSES

The final cause is the purpose or the end of a thing, the last "instance" in the causation of a certain effect. We regard as the final causes of peptic ulcer the factors which whip the neuro-secretory apparatus into an excessive or disordered activity. This dysfunction may affect either the peripheral or the central nervous system.

1. *Peripheral (Mucosal) Nervous Irritation.* When we reviewed the occasional causes of ulcer, we asked the question whether a constantly repeated injury to the mucous membrane could not set up a chronic irritation of the peripheral nerves and in this way start an excessive secretion of gastric chyme. This may be possible. Yet, when we consider the abuse to which many alcoholics subject their stomachs without showing signs of ulcers, and remember the excessive use of spices by certain races, without apparent increase in the incidence of gastric ulcers, we hesitate to raise these occasional occurrences to the dignity of a final cause. If we correct the diet of these people, the majority of them get better, but in many the symptoms persist, showing that other forces are at work to keep up the abnormal secretion of acid.

II. *Reflex Irritation of Abdominal or Peritoneal Origin:* In another group of cases, the nervous dysfunction has its origin in some residual focus of peritoneal inflammation, chiefly in the appendix, gall bladder, or pancreas, but also — though rarely — in the pelvic organs, in diverticula, in the kidneys, etc. We regard these not so much as possible foci of infection, as we do sources of irritation resulting from inflamed organs with contents under tension, stenosis of the walls, kinks, or firm adhesions to important structures (intestine, ureter, nerve trunks, etc.). Any of these states of chronic peritoneal irritation may cause some reflex neurosecretory disturbance with reflex dyspepsia and hyperacidity, reflex pyloric spasm, cramps and all of the symptoms of peptic ulcer, including hemorrhage. Such reflex irritation as a cause of peptic ulcer has been accepted by many authors (7, 16).

Among our patients with ulcer, we meet a certain number of persons of primitive type—laborers, farmers, etc.—who lead a sort of "vegetable" life, doing no thinking, having no cerebral activity or mental worry of any kind. It is evident that, in people of this type, the nervous disturbance of secretion cannot be explained by any influence of the central nervous apparatus but is caused by reflexes originating in the abdomen. Some of these patients are so dull in their sensations that, occasionally, we are called to see them for hemorrhage or a perforation as a first sign of an ulcer of which they had no slightest premonition. It should be remembered, however, that foci of chronic peritoneal irritation may also exist in the intellectual persons along with the disorders of the central nervous system. At any rate, it is our duty, especially in patients of low mental development, to search diligently for residual inflammations in the peritoneum as possible sources of these reflex phenomena; it is only by eradication of these old inflammatory lesions that the gastric symptoms can be relieved in patients of this group.

III. *Central Nervous Disturbances:* In this very large group of patients, with functional disorders of the central nervous system, the final cause is represented by all the noxious factors of modern life which keep our brains in a state of continual tension: economic and financial fears and worries; heavy responsibilities; cut-throat competition; the necessity of doing things at great speed with undue excitement; lack of rest and of sufficient relaxation, especially during the time of digestion. The central nervous system, struck by the constant pounding of these injurious forces, will itself repercuss on the different organs along certain paths; why this repercussion should, in certain cases, fall on the stomach, in others on the intestine, or the heart, or the thyroid, we do not know. We study its action on the gastro-duodenum here solely because we are especially interested in this aspect of the problem on account of its frequency at the present time.

Prophylaxis: Owing to the enervating influences of the present day, we have become an emotional race craving sensationalism and thrills of all kinds. We yield too quickly to excitement and to uncontrolled impulses. It should be possible by education, by mental hygiene, and special training to cultivate in our children strength and firmness of character, as the ancients did, so as to permit them always to keep their nervous balance in adverse and difficult situations.

The Management of Cerebral Activities in Patients with Ulcer: Some writers—Von Bergmann (11, 15), Rivers and Dry (17), and others have already advocated the control of the neurogenic factors in the treatment of this disease. I go further; I believe that the brunt of our attack should be directed against these final causes constantly injuring the nervous system, and that the patient should be given much more detailed and specific instructions as how to regulate his mental activities, especially during the periods of digestion.

Major shocks such as the death of a relative or friend, financial reverses, severe bodily injuries, are all fraught with great danger as they may lead to a prolonged acid crises with hemorrhage, disability, etc.

In such occurrences the physician and the family of the patient should do their utmost to divert his mind, soothe his pain, and encourage him in any possible way. A trip or a change of environment may be very necessary at such a time.

Outside of these great misfortunes, however, there are all the minor shocks and annoyances of every day life: errors, delays, interruptions, trifles of all kinds, details of work that may be left to a secretary, and much unnecessary excitement that one should avoid. There are also matters involving our personal pride and ambition, speculation, gambling, etc., and risks of every kind. The patient with ulcer should leave these things severely alone. By planning and determination he should learn to keep away from all non-essentials, thereby reducing the sources of irritation to the minimum so as to preserve the tone and fitness of his nervous system.

The Division of Work: As a general rule, heavy mental work should be done as late as possible after meals, or only after a very light meal.

Mental activities should be divided in two parts: (a) the routine work might be started one hour after meals, and (b) the strenuous work that should not begin before three hours after meals. If this cannot be done, the midday meal should be much curtailed and the patient could eat more at night when he is through with his duties. Personally, I like to do any heavy work, such as reading an important book or paper, preparing a speech or memorizing a lecture, drawing the final conclusions of an article, etc., early in the morning between five and seven; two hours of cerebral activity of this kind are enough and the rest of the day should be given to routine work only. For a business man who has to do his most concentrated thinking in the middle of the day, things may have to be arranged differently; it is better for him to sleep longer in the morning, have a quiet breakfast, walk leisurely to his office, a part of the way at least; then begin the day with the routine work, looking through his mail or talking to employees about his affairs in general, etc., reserving the more strenuous work for the hours from 11:00 a.m. to noon, and 4:00 to 5:00 p.m. If the pressure is such that heavy work, important conferences and the like must be resumed early in the afternoon, a very small lunch or no lunch at all should be taken.

The meal hour should be spent in pleasant company and in light conversation: some men invite their friends to lunch in order to discuss serious problems; some even have that meal served on a tray in the office while they keep studying important matters. No wonder their digestions are disorganized! The best plan would be for the patient to lie down or have a quiet stroll after meals; at least there should be no exertion at that time.

The Question of Rest: The evening should be left to relaxation, quiet games, etc., and a man should certainly not select a hobby that is more strenuous than his regular occupation as some people do.

Those who can afford it should take a complete week-end rest or a vacation as often as possible.

Mental rest and relaxation should be the keynote in the treatment of peptic ulcer.

The execution of the foregoing program may prove a very arduous matter for the physician in charge; he must secure the cooperation of his patients many of whom will say to him, "It cannot be done." This disease is so hidden and so insidious that they will not see it; they will not admit it; some will rebel and throw away all dietetic restraint. We even see physicians adopting this foolish attitude—as if the fact that we ignore an organic lesion could contribute to its cure! If such a man finally suffers a severe complication, a prolonged acid crisis, or a profuse hemorrhage, with months and years of enforced idleness, he will become more amenable to reason and persuasion. If he has to provide for dependents, he will see that in order to live and to work a few years longer, our plan is worth something after all, even if it entails heavy sacrifices of his pleasure and his mode of life and, by trying, he will find that it *can* be done.

In this last chapter, we have merely sketched the general plan of treatment. If an alert internist or neurologist would undertake this task of drafting a schedule of work, designed to protect the local function of digestion from the disturbing influences of the central nervous system, and do it in such a way that it could be adapted to the different professions, according to their special requirements, he would render a signal service to the business world in general.

SUMMARY AND CONCLUSIONS

1. An attempt is made, by following the ancient classifications, to analyze and evaluate the various causes of peptic ulcer.

2. The material cause—the biological structure of the tissue—may still be considered an uncontrollable factor.

3. The occasional cause—changes in the tissues arising from trauma or circulatory disturbances—are important, but it is doubtful whether they can start an ulcer in the absence of abnormal acidity.

4. The formal cause—the shape of the stomach and the mechanism of the pyloric sphincter—is treated by various types of surgical operations which do not obtain an absolute percentage of good results because they act only indirectly on the efficient cause (secre-

tion of acid) and do nothing for the main or final cause.

5. The efficient cause — hyperacidity — is counteracted by our dietetic prescriptions, but the results are often incomplete because this therapy also does not affect the final cause. Attention is called to the "bad timing" of the acid secretion as an essential feature and to the appearance of prolonged acid crises. Emphasis is laid on the neurogenic theory.

6. The final causes are discussed and a possible line of treatment is suggested regarding the regulation of mental activities in such a way as to protect the local mechanism of digestion against the inroads of the central nervous system.

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Intestinal Motility in Rats Anesthetized with Ether*

By

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IT has been demonstrated through fluoroscopic observations (1) that ether and chloroform anesthesias are accompanied by a decrease in tone and arrest of movements of the entire gut. Miller (2), working with dogs having balloons in permanent fistulae of the stomach, small intestine and colon, has shown that with ether anesthesia all stages are accompanied by diminution or loss of tone and contractions except the transitory so-called "excitement," or delirium stage. During surgical anesthesia he found both complete inhibition of most of the smaller contractions and entire lack of peristalsis, as noted at all three fistulae. Sleeth and Van Liere (3) have demonstrated a marked increase in gastric emptying time of etherized animals. Following anesthesia, Miller (2) found that the colon may become hypertonic or spastic and that the small intestine shows exaggerated activity, while the stomach may remain somewhat atonic for five hours or more.

Macht's method (4) of studying intestinal motility in rats was introduced as a technique for the comparison of cathartics, but is equally well suited for studying other factors influencing intestinal motility. Like the roentgenographic methods, it measures only the *effective* motility of the gut, and so is perhaps more likely to yield results applicable to practical conditions in the human than are some of the other physiological techniques. In order to obtain a quantitative picture of the effect of ether on effective intestinal motility, Macht's technique was used in the following experiments. No variations were made from the technique as previously employed (5).

EXPERIMENTAL

Ten rats, weighing approximately 200 Gm., prepared through a standard treatment, were given 2.0 c.c. of a charcoal emulsion in gum acacia solution intragastrically and were sacrificed by a blow on the head 50 minutes after administration of the charcoal. The progress of this test meal in the intestinal tract between the pylorus and anus was measured and calculated in per cent of the tract traversed. The average value for these 10 control animals is noted in Table I.

Similar groups were treated likewise: (a) 10 minutes after induction of ether anesthesia in a chamber of 18 L. total capacity, containing an initial concentration of 2.5 mM L. of ether in oxygen; anesthesia with the same tension of ether was then resumed and continued 50 minutes, when the animals were sacrificed and examined; (b) immediately after 60 minutes of anesthesia with the same initial concentration of ether; and (c-h) at various periods after anesthetization for one hour with ether at the same initial tension, up to 48 hours. Averaged results for each group of 10 animals are collected in Table I.

As the rats were of approximately the same body weight in all groups, and the same number of rats was used in each group, the depth of anesthesia over the period of an hour may be considered very nearly the same for all groups since variations in the amount of ether absorbed by the rats would be negligible. Objectively, no difference in the depth of anesthesia of the various groups could be noticed. In all cases, the ether mixtures were made up with oxygen, and accumulation of carbon dioxide in the anesthesia chamber prevented by keeping a large gauze bag of moist soda-lime in motion during the period of

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anesthesia. The effectiveness of these measures in preventing anoxemia or excess of carbon dioxide is reflected in the results collected in Table I.

DISCUSSION

From Table I, it may be noted that suppression of effective peristalsis in the small intestine is very marked during the period of anesthesia. In only one case did the test meal traverse more than 10% of the intestinal tract during anesthesia. Measurement of the passage of the test meal was difficult in animals tested during the first hour after anesthesia, since scattered small portions of the test meal, which appear as small specks through the intestinal wall, were carried along to about half the length of the intestine in a small number of rats and so increased the average figure. The value obtained for motility during the first post-anesthetic hour is therefore probably misleadingly high, due to the occurrence of weak peristaltic rushes toward the end of the test period.

Only in experiments done in the second post-anesthetic hour and thereafter is the normal appearance of a solid column of material contained in the gut obtained, denoting the resumption of normal strong peristalsis. This delay in recovery of intestinal tonus and peristalsis is not surprising, for the rats remain lightly anesthetized for as long as 20 minutes after ether administration is stopped, indicating that the tissues have become well saturated with ether during the long period of deep anesthesia.

The use of 10 animals for each test by Macht's technique has been recommended, and a comparison of control values in Macht's (4) and other (5) series with the present findings indicates that excellent agreement may be obtained using this number. Tolerances noted in Table I represent one standard deviation of the mean. It may be noted that only the experiments done during anesthesia and the first, second and sixth post-anesthetic hours differ significantly from the controls.

TABLE I

Action of ether on the motility of small intestines, Macht's Method. Results expressed as per cent of intestinal tract between pylorus and anus traversed by a test meal in 50 minutes

Untreated	During Anesthesia	Hours after 60 minutes anesthesia						
		1st	2nd	3rd	6th	12th	24th	48th
55 ± 2	3 ± 1	30 ± 3	48 ± 2	60 ± 2	63 ± 2	57 ± 3	57 ± 2	55 ± 3

SUMMARY

Surgical anesthesia with ether inhibits the motility of the small intestine of rats for the period of its duration. Recovery is rapid after anesthetization with ether for one hour, and the gut regains approximately its normal activity by the second hour after anesthesia is terminated. Some slight hyperactivity may occur from the third to the sixth post-anesthetic hours.

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Editorials

NEWER METHODS OF TREATING HEMORRHAGE DUE TO ULCER

AT the 16th Scandinavian Congress for Internal Medicine held at Uppsala in 1933, Meulengracht made his first suggestion and reported his first results obtained by treating hematemesis and melena by giving the patient "something to eat." Subsequently, in 1934 and again in 1935 he reported larger series of cases with exceptionally good results in spite of his seemingly radical procedure of continuing a full and varied diet throughout the period of active hemorrhage and during the post-hemorrhage convalescence. He treated 251 ulcer cases with only 3 deaths, a truly splendid record (1.2%). The diet consisted of pureed and soft foods and the free administration of alkalies. Dinner alone included meat balls, broiled chops, omelette, fish balls, vegetable soup, stewed apricots, apple sauce, the patients eating "as much as they want."

This is a brave, very brave, frontal attack upon hemorrhage by the manoever of free and plentiful feeding, a procedure which affronts our previous orthodox concepts of enforced rest for the injured parts, physiological quiet, the free use of morphine and abstention of all food and drink by mouth. But since this is the day of radical attack upon orthodox tradition, it behooves the older members of the conservative party to pay close attention and weigh carefully the merits or demerits of such a proposal before accepting it precipitately or denouncing it without trial.

Meulengracht has quoted the mortality figures for the treatment of ulcer hemorrhage by various older authors as Bullmer 10.7%, Chiesman 25%, Tidy 19%, Hinton 20%, Lynch 12.9%. This is of course painting a very black picture, hardly consonant with all the facts.

Thus Chiesman as recently as 1932 had a mortality at St. Thomas' in London of 27% of 191 cases, but

transfused only 15 patients! At least 36 patients died of fatal hemorrhage without transfusion. The series of Lynch comprised only 31 cases (12.9%) mortality); that of Hinton, 50 cases (20% of deaths), both series being rather small and exceptionally unfortunate.

On the other hand, with the older methods of starvation and sedation, Hurst reported a mortality from Guy's Hospital, also in London, of 2.5% of 600 cases; Nielsen, also from a Scandinavian country, one death in 182 ulcer cases, Paterson, 3.8% mortality in 124 cases, and Crohn and Manheim, a fatality rate of 4 deaths in 94 gross ulcer hemorrhages 4.2%.

It is true of all such controversial medical literature that figures can often be cited to uphold a viewpoint, and another set of figures to confound it, each of the parties acting in good faith and citing authoritative publications. But if nine justices can divide frequently five to four on an interpretation of a statute, how easily for medical men to differ when attempting to decide upon a point of applied rather than pure science, when hoping to draw the truth from a concise publication tinctured by the personality and biases of the writers.

A word of caution before applying this newer philosophy of free feeding to freely bleeding ulcers might well be in place. The older methods of starvation and rest were apparently very satisfactory in the hands of the older experienced physicians. It was a sagacious generation that had learned by bitter experience that to feed during the lull of a fast hemorrhage was often to invite a brisk recurrence perhaps with fatal issue.

Science is never a closed page, anyone has the right to reopen an issue for reconsideration. But before the left-wing radicals put into large-scale practice this rather novel suggestion of full feeding, it might do well to stop and ponder possible direful consequences of such a seemingly rash procedure.

No one would question the brilliant therapeutic results of Meulengracht himself in skillfully feeding gross hemorrhage; no one need question the past experience of physicians who starved and rested their bleeding patients with most satisfactory results.

It is to be feared that a sudden reversal of an accepted cautionary practice may, in the hands of clinicians less experienced than Meulengracht, lead to results that may be unfortunate.

This is meant as a word of caution rather than as a discouragement of a therapeutic suggestion.

Burrill B. Crohn, New York, N. Y.

HOW DO BULKY FOODS RELIEVE CONSTIPATION?

THERE is still need for information as to the way in which certain substances given by mouth increase the bulk of the stools or otherwise relieve constipation. Thus one commonly reads that hydrocarbon oil relieves constipation by lubricating the bowel, but anyone who has ever watched the muscular contractions of the bowel and the way in which the fluid contents are moved onward from one segment to another will find it hard to see how lubrication can possibly help the process. In fact it should hinder it much as a slippery field makes it harder for a football team to push onward toward the goal. Lubrication could be of service only if a solid cylindrical plug were moving through a rigid tube with a diameter slightly greater than that of the plug.

Actually the surface of the bowel is well lubricated with mucus and other secretions, and if it were not it still would be hard to see how the taking of oil could facilitate the movements of liquids through a soft muscular tube which contracts peristaltically. It is doubtful if anyone yet knows just why hydrocarbon oil tends to relieve constipation. Perhaps it helps partly by producing a more cylindrical stool which can be extruded more easily. According to Contoléon and Joannidès (1), and Mellanby (2), it may act also by interfering with absorption in stomach and bowel. This interference with absorption may account for the observation of some persons that a dose of hydrocarbon oil, taken before a cocktail party, will go far to give that extra tolerance for alcohol which is so greatly desired by many.

But more important than physical factors may be the chemical ones. Thus there are reasons for believing that the chemical composition and the pH of the fecal residues as they reach the rectum can have much more to do with causing or relieving constipation than does the bulk or consistency of these residues. As every person knows who has ever suffered with constipation, the dry, ovulated type of stool seems to be quite without that stimulating effect on the mucosa of the rectum which normally tends to start the process of defecation.

At other times, in the same person, the feces will so irritate the rectum and so stimulate the defecatory reflexes that evacuation can be restrained only with considerable discomfort, or a soft stool will be so irritant that defecation cannot be put off for more than a few minutes. Significant, doubtless, is the fact that when such material is voided the anal ring often feels scalded and raw as if it had been burnt by some escharotic.

There is still need for research that will show what the substances are which so stimulate the rectal mucosa. One would like to know where and how they are formed, and, if they come from the upper part of the small bowel, why they are carried down unchanged into the colon. Moreover, why is it that some diarrheic movements do not irritate the anal ring while others seem to the patient to be full of Cayenne pepper?

A number of observers have puzzled also over the surprisingly large increase in the bulk of the stool which can sometimes be produced by giving a small amount of agar or other hygroscopic substance. When they applied quantitative methods to the problem they found that sometimes the increase in the bulk of the stools was larger than what could be accounted for by any amount of water which could possibly be imbibed by the quantity of gummy substance given. The puzzle became even greater when it was found that more than half of the supposedly indigestible jelly had been broken up by bacteria and lost on the way through the bowel.

There is another curious puzzle which has not yet been faced and studied as it should be and this is why, when one starts taking agar or some other bulk matter, one often for a while gets an excellent laxative effect, with voluminous stools, and then, after a few days or weeks, becomes constipated. Evidently the bowel is

able to make some adjustment so that it can take the water away from the hygroscopic substances used. Much work needs to be done on this problem because here lies one of the worst stumbling blocks in our therapeutic path. The constipated can often be relieved, but many fail to stay cured unless perhaps the physician is wise enough to have them shift every two weeks or so from one type of bulk producer to another.

Most helpful and thought-producing are some studies made during the last few years by Olmsted and his associates. In beginning their investigations they had first to work out a satisfactory method of measuring the amounts of cellulose, hemicellulose and lignin in foods and feces. Unfortunately, in the past, these three groups of substances have been lumped together under the heading of "crude fiber," and worse yet, the method used for estimating crude fiber in foods and fecal residues did not give accurate results. As Olmsted has now shown, it is important that vegetable roughage be divided into celluloses, hemicelluloses and lignins because they differ not only in the way in which they go through the digestive tract, but also in their ability to increase the bulk of the stool, and therefore in their value in relieving constipation.

Of the three groups of woody substances found in vegetable foods, the hemicelluloses are the most easily broken down by the bacteria of the bowel. Some of the end results of this fermentation, identified as fatty acids, appear to supply about a quarter of the caloric needs of grazing animals.

Curiously, Williams and Olmsted (3) found that pure cellulose is not a good substance for the relief of constipation because it hasn't much power to hold water and thus to increase the bulk of the stools. Taken in the form of cellu flour about 7 per cent of the cellulose disappeared in the stools of the medical students who served as test subjects. Only from 3 to 12 per cent of the lignin in food disappeared, but of the hemicelluloses, up to 80 per cent disappeared on the way through the bowel.

Agar, which is about 80 per cent hemicellulose, did not disappear in the bowel to the extent that one would think it would because of its composition. Actually in some experiments only 48 per cent of the cellulose and hemicellulose of agar disappeared. Perhaps because agar is able to hold much water it proved to be the most effective of the several substances experimented with in increasing the bulk of the stool and relieving constipation.

It appeared, however, that this effectiveness of agar was not all due to its hygroscopic property. Much of its laxative effect seemed to be due to the retention in the stools of some of the lower volatile fatty acids which result from the bacterial digestion of the hemicelluloses. As is well known to pediatricians, fatty acids in the stools can have a laxative effect. Puzzles remain, however, because those who have put fatty acids into the lumen of the bowel of animals have not always observed a stimulating effect (4, 5).

More work needs to be done also before it is known why certain fruit juices and certain fruits such as prunes and figs are mildly laxative. Some experiments made years ago with prunes and other fruits made me suspect that the pectins may be responsible for some of the laxative action. Curiously, commercial solutions of pectin seemed to be decidedly laxative for some persons but not for others. Recently some experiments have reported the presence of a laxative in concentrated prune juice. Years ago when I searched for it I could not find it.

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A PLEA FOR CONSERVATISM IN THE INTERPRETATION OF GASTROSCOPIC FINDINGS

DIRECT visualization of the interior of organs connected with the various orifices of the body has increased the accuracy of diagnosis and has broadened the field for efficient therapy.

The most recent instrument of this type which has been introduced is the Wolf-Schindler gastroscope. The ease and safety with which this instrument can be passed into the stomach and the excellence of the views of the gastric mucous membrane which may thus be obtained make gastroscopy desirable in many patients who suffer from disorders referable to the stomach. As with other similar innovations in medicine, there is a tendency to overemphasize the importance of insignificant changes which may be observed and to attribute many symptoms to these apparent deviations from normal. One must remember that symptoms referable to the gastro-intestinal tract occur with great frequency in patients who suffer from nervous instability. To attempt to attribute these symptoms to "gastritis" on the basis of minimal changes in the mucous membrane of the stomach, which may sometimes be observed through the gastroscope, will lead to disappointment in treatment and will serve to discredit an instrument which appears to have value in the more accurate diagnosis of gastric diseases.

Porter P. Vinson, Richmond, Va.

THE PLASMA PROTEINS AND LIVER DISEASE

HYPOPROTEINEMIA is, as a rule, the result of one of three conditions: inadequate dietary intake or actual starvation, unusual losses of protein due to albuminuria or severe diarrhea, or failure of intestinal absorption of protein-forming substances, as noted in sprue or in the presence of gastrojejunocolic fistula.

The idea that hepatic lesions might be attended by alterations in the plasma proteins is relatively new, but there are a number of clinical reports now available which indicate that hypoproteinemia is a fairly constant finding in parenchymatous disease of the liver. In extreme conditions, very low levels of plasma proteins may be found, with albumin-globulin ratios as low as 0.3. In the earlier reports it was assumed that this finding was due to malnutrition, but a review of some recently reported cases indicates that the reduction in circulating protein is not due to abnormal losses, to an inadequate dietary intake, or to lack of absorption. In fact, it has been clearly demonstrated

that a diet high in protein, producing a strongly positive nitrogen balance, does not necessarily increase the proteins in hepatic disease; it has also been shown that losses in ascitic fluid do not materially reduce the plasma levels. By exclusion, therefore, the observed reductions appear to be due to the inability of the body to fabricate these substances, particularly serum albumin, and the liver appears to be responsible in part.

There is considerable experimental evidence to show that this explanation is sound. Reductions in total serum proteins have been noted after experimental injury of the liver and in animals with Eck fistulas. Recent studies from Whipple's laboratory seem to indicate that there is a reserve of protein-building material in the organism which is stored in large part in the liver, and that a large portion of this is either in the form of albumin or of albumin-producing material. It is not, of course, inferred that the liver is the only site of protein synthesis, but there is good reason to believe that the liver probably figures in some mechanism by which a dynamic equilibrium is maintained between stored and circulating protein.

These changes in plasma proteins may have considerable diagnostic and prognostic significance. In recent uncomplicated obstructive jaundice, such as that produced by neoplastic obstruction of the bile passages, the total protein and the albumin-globulin ratio are usually within normal limits. When ascending biliary infection or obstructive cirrhosis complicates the picture, the total protein is definitely reduced and the albumin-globulin ratio decreases steadily. In the severest type of acute parenchymatous hepatic injury, such as that seen in portal cirrhosis, the total protein may be low, the so-called edema level, and less than 25 per cent of the total amount will be albumin. These changes are reversible and normal values for total protein and albumin-globulin ratios are found as recovery takes place.

Enough is known of the relation of plasma proteins to the distribution of the body fluids to assure us that the low levels seen in hepatic disease are not without some effect on the production of ascites and edema. Physical measurements appear to show that the albumin component of the plasma proteins is chiefly responsible for their osmotic effect, the globulin fraction being relatively unimportant. While it must be admitted that the "salting" process by which the two proteins are separated is somewhat imperfect, the error of the method is probably not as great as the variations which have been observed in clinical cases. Recent measurements of the osmotic pressure of the serum of patients with hypoproteinemia secondary to hepatic injury indicate not only that the total osmotic pressure is low, but that the unit pressure per milligram of nitrogen content is also reduced. It seems quite likely, therefore, that the development of ascites and edema in hepatic disease depends, to a large extent at least, upon changes in the serum albumin and upon the effects which such changes produce on the osmotic pressure of blood serum. Quite possibly, as Rosenberg has noted, the increased size of erythrocytes, which may be observed very early in the course of clinical cases of hepatic injury, is due to this same decrease in osmotic pressure.

There are so many unknown factors in regard to hepatic insufficiency that any studies of these alterations in circulating protein and the effects on water and electrolyte distribution secondary to them cannot fail to give information of clinical and physiologic importance.

A. M. Snell.

BRIEF REVIEW OF THE PAST AND FUTURE OF GASTROPHOTOGRAPHY

IN the development of gastrophotography two distinct periods may be distinguished. In the first period the chief goal was that of safely establishing a morphologic method for the diagnosis of lesions of the gastric mucosa. Lange of Munich was the first to introduce a small photographic camera attached to the tip of a rubber tube into the stomach (1898) (1). By the development of the rigid gastroscope a multitude of pathologic pictures was revealed and became known, especially by the publication of my gastroscopic "Atlas" published in 1923 (2). Since gastroscopy with the rigid gastroscope was a dangerous method, safe only in the hands of a few experts, the efforts to come to another morphologic method for diagnosing gastric diseases were continued. I greeted the invention of the gastrophotor (1929, Heilpern, Back and Porges) (3) with greatest enthusiasm, and for three years I tried to photograph the interior of the stomach. Henning, of Leipzig, did the same. It seems that we were the only workers to check gastrophotography by gastroscopy with its distinct and undeniable pictures, but both of us after long efforts decided that the method was unreliable and of no use at all (4, 5). There were three difficulties: (1) One never knew which region of the stomach had really been exposed, a drawback, foreseen as early as 1897 by Kelling, and one which could be overcome only by photographs taken through the gastroscope: "aimed exposures." (2) The pictures were generally blurred. This obstacle could be overcome by further development of the apparatus. The newest book of Heilpern, and also most of the recent papers are as disappointing as were the first books by Bécart (6) and Bernay (7) (both 1931), but Garin and Bernay, of Lyon, are now working with a Lens-bearing apparatus, and pictures shown by Rehfuss, Philadelphia, were entirely sharp. (3) The most color-sensitive or panchromatic films were not able to reproduce the slight differences in color in the decisive part of the spectrum between yellow and red, which are of the greatest diagnostic importance. In one of my papers (8), I reproduced the picture of a large benign ulcer, a photograph made through the rigid gastroscope with Henning's camera. The surface of the ulcer, gastroscopically brilliant yellow of color, was the same grey as the adjacent mucosa which gastroscopically was orange-red. The ulcer could be recognized on the film because of its one undermined edge casting a dark shadow. After the introduction of the flexible gastroscope, gastrophotography with the blindly working gastrophotor has become obsolete as everybody will notice who has worked for years with both methods. Based on the numerous findings with the flexible gastroscope a new "endoscopic pathology" of the stomach has developed. Gastrophotography, in its present stage can not even try to imitate these most definite results. The fact that gastroscopy is an office procedure and has spread as such, in a few years over all countries with unbelievable rapidity proves that

gastrophotography now has come into a second stage. The black and white picture cannot compete with the easily obtained direct aspect of the colorful gastric mucosa, but it may provide us with *objective records* of at least a part of our gastroscopic findings. This can be done only by photographing through the flexible gastroscope. Until now the light of this instrument was not sufficient to permit aimed photography, but this is a minor technical question to be solved in a short time. This type of photography would not be of diagnostic value, but it would give us some permanent records. Entirely satisfactory results will not be obtained in the near future. It is important that neither the urologists nor the proctologists routinely photograph their findings although this type of photography would be much easier than gastrophotography, because the mucosa of the bladder and of the rectum do not move as the gastric mucosa does by the respiratory movements of the stomach. All depends as to whether films of sufficient color sensitiveness will be available. It seems unlikely that colored films will be sufficiently sensitive in the decisive part of the spectrum. The psychological question remains: why do the urologists care so little about making photographs in cystoscopy, while some gastro-enterologists advocate the more difficult photography of the stomach. Evidently they have not as yet realized that they have now an instrument with which they can inspect their organ as successfully as the urologist does the bladder, and that in the great majority of all cases this examination is much less disagreeable to the patient than is cystoscopy in the male. Nevertheless we certainly will continue with our efforts to get documents as objective as the X-ray film, but we will choose that way which alone provides success: photography through the gastroscope.

Rudolf Schindler, Chicago, Ill.

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The Bowel . . . A source of infection

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Abstracts

ALLEN, ARTHUR W. AND HOWE, HENRY F.

"The Relationship of Calcified Mesenteric Glands to Abdominal Pain." South. Surg. Jour., 5:447-462, Dec., 1936.

Enlarged mesenteric glands in children or adolescents should be classified as either "acute mesenteric adenitis" or 'calcified quiescent tuberculous glands." The symptoms of the former may mimic an acute appendicitis and generally subside after an exploratory laparotomy or appendectomy. They present an entirely different clinical picture from the calcified tuberculous glands which must be considered in atypical cases of chronic or recurrent appendicitis. While these glands are usually demonstrated by an X-ray ex-

amination of cases with questionable diagnosis or by exploratory laparotomy physical examination of the abdomen will show tenderness over the involved glands. The most common area is just above McBurney's point but may extend upward and to the left along the root of the mesentery. Occasionally a definite mass may be felt but there is little if any spasm of the abdominal wall and there is no rebound tenderness. Approximately 50 per cent of patients showing calcified glands will have no symptoms attributable to them and will generally respond well to general hygienic treatment. This is also true of those with mild symptoms especially if the patients are quite young. Many of those having symptoms will have rather frequent attacks of pain usually, however, of only a few hours duration.

In a well-studied small series of cases involving young adults it was definitely shown that a decidedly higher percentage of cures was obtained when these calcified glands were removed at the time of appendectomy. A warning is given regarding the technique of removal; the integrity of the blood vessels of the mesentery must be maintained and no rough area left uncovered by peritoneum. The persistence of symptoms in about half of the cases where the glands were not disturbed is a fact worthy of careful consideration. Fortunately other tuberculous foci in the body are quite rare in this type of infection.

J. Duffy Hancock, Louisville.

GOLDBURGH, HAROLD L.

Amebic Abscess of the Liver: Report of a Case Without Previous Manifestations of Amebiasis: Operation and Recovery. Ann. Int. Med., Vol. X, p. 926, Dec., 1936.

The author reports a case of amebic abscess of the liver without previous manifestations of amebiasis, with operation and recovery.

The patient, a white male, age 58 years, entered the hospital September 16, 1935, and claimed that a week previously he had noticed a sudden onset of severe pain in the right upper abdomen, griping in character, coming on every hour or hour and one-half and lasting for fifteen minutes. The pain had no relationship to food and was not associated with nausea, vomiting or diarrhea. He had persistent hiccoughing; was chilly, had fever and felt drowsy. The past medical history was essentially negative, and there was no history of contact with carriers.

After the operation and after a month of repeated questioning, the daughter stated that for a period of fifteen years the patient had had recurrent pains in his right upper abdomen. There were attacks of abdominal cramps without diarrhea, coming on twice a week and lasting 24 hours. These pains were relieved in one hour by the taking of a tablespoonful of coal oil with sugar. His son-in-law, who lived in the same house, had been treated for two years for bloody diarrhea, but repeated examinations of his stools had failed to reveal the presence of ameba.

Physical examination: The patient was a slightly emaciated and dehydrated adult male, who appeared distressed. The abdomen revealed moderate fullness in the epigastrium, over which area there was pain and tenderness which was made worse upon breathing. The upper limit of the liver dullness commenced in the fifth intercostal space anteriorly in the mid-clavicular line and extended 6 centimeters below the costal border. The spleen was not palpable and there were no signs of fluid in the abdominal cavity. Other physical signs were negative.

The temperature ranged between 100.4 and 102.1 F. The first blood count was: Hb. 14 gm.; r.b.c. 3,840,000; w.b.c. 16,000 per cu. mm.; polymorphonclears 96 per cent. Of the latter 26 per cent were segmented and 70 per cent were stab forms. Lymphocytes

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were 2 per cent; monocytes 2 per cent. There were no eosinophiles.

A diagnosis of acute suppurative cholecystitis with secondary hepatitis was made and a laparotomy performed. A normal gall bladder and spleen were found, but the right lobe of the liver had a nut-meg appearance and contained an abscess. Aspiration of the latter yielded 10 ounces of a thick, creamy, slightly brownish pus. A catheter was introduced and sutured in place.

Examination of the pus revealed Endameba histolytica and culture revealed *Bacillus coli*.

Two days later symptoms subsided and the temperature became normal; within seven days the catheter draining the abscess was removed; the wound healed and convalescence was uneventful. Amebicidal therapy was instituted upon the patient's return to the medical ward and he was discharged clinically cured, November 21, 1935. Before the patient's discharge, ten stool examinations and duodenal drainages were negative for ameba and cysts. Proctoscopic examination showed no evidence of ulceration, but the X-ray appearance of the colon was suggestive of some inflammatory process involving the cecum.

Accompanying the author's report there is a short review of the literature contrasting the geographical incidence of amebiasis. Craig states that 5-10 per cent of the American population harbor this infestation, while in Philadelphia at the Jefferson Hospital during the last decade there was one case among approximately 120,000 admissions and 3,000 autopsies, and at The Philadelphia General Hospital among approximately 232,000 admissions and 24,000 autopsies there were five proven cases.

It must be remembered that in a high percentage of cases the first symptoms of amebiasis may be an abscess of the liver, and the time elapsing between the infestation and the appearance of the liver abscess may vary from a few months to many years. In the absence of a history of amebic dysentery the primary lesions, in the majority of instances, can be located in the cecum and ascending colon, which would produce no diarrhea.

The medical and surgical therapy is briefly discussed.

B. B. Vincent Lyon and Charles W. Wirts, Jr., Philadelphia.

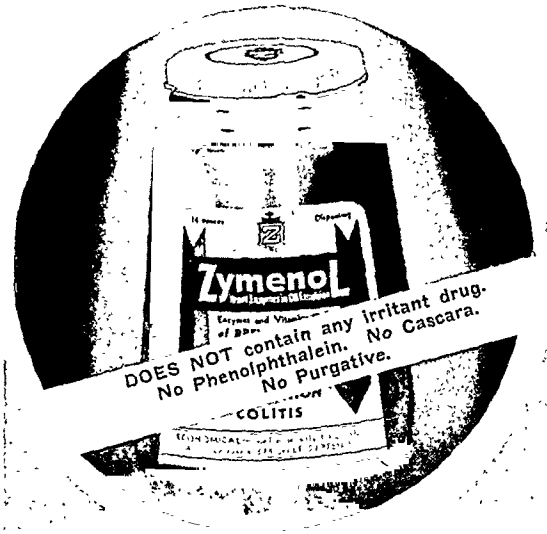
KUHLMANN, FRITZ.

(The Radiology of Diseases of the Small Intestine). Dünndarmstörungen im Röntgenbild. Fortschritte auf dem Gebiete der Rontgenstrahlen, 54:5:433, Nov., 1936.

Disturbances of the small bowel generally play only a small part in respect to practical diagnosis. The chief factors of diagnosis of small bowel conditions are the history, palpation, especially the determination of points of tenderness, investigation of the feces and X-ray investigation. Investigation of the feces in the majority of cases gives no definite results as, during the passage of the feces, via the colon, changes which originated in the small bowel become masked. The essential means of diagnosis, apart from the history, is the radiological investigation of the small bowel.

Before information can be derived concerning pathological conditions, the appearances of the normal small bowel must be known. The author deals with the superimposition of the small bowel contents in a surface projection and the effect of excessive secretion which can give rise to loss of definition of roentgenograms.

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be recognized as defects of motility, an acceleration of the passage of contents, obstruction of the passage of contents and defects of tonus, namely hypertonus and atony (diffuse and localized), hypersecretion and lack of response to the stimulation of the barium meal. In other small bowel disturbances there is abnormal development of flatus, which is particularly described in respect to the ileum. Mucosal relief investigations in disease of the small bowel are of little value owing to the great complication of the normal relief appearances. In inflammatory conditions there are disturbances of the appearances owing to the long continued non-movement of the mucous membrane when inflammatory swelling is present.

After describing the general symptome of disease of the small bowel, particularly chronic enteritis, the various subsidary types of the disease are dealt with. The types of pain experienced by the patient are compared as to type, degree, localization and the period of their occurrance in relation to the radiological findings.

James T. Case.

SCHEIBEL, OVE.

Concerning Pitressin in Roentgen Examination of the Abdomen as an Agent for Reducing Shadows Caused by Intestinal Gas. Acta Radiologica, 17:511, Oct. 31, 1936.

Aside from true ileus in which the amount of gas in the intestine and the distribution thereof are of great importance in roentgen diagnosis, it is mainly in the X-ray study of the urinary passages that one finds large amounts of gas in the intestine interfering with the roentgen-ray study. Particularly in renal colic gas may be present in such quantities that it resembles ileus, or rather reflex ileus, which can be taken for true ileus. At the Bispebjerg Hospital attempts have been made to reduce intestinal gas content by various dietary measures, such as laxatives, enemas of various kinds, an esophageal tube passed into the stomach to prevent swallowing of air, etc. Finally experiments were done with pitressin, a constitutent of pituitrin, carried out in patients in whom intestinal gas accumulations caused inconvenient shadows.

The gas content of the intestine depends on whether the patient is recumbent or erect. It is explained that in the recumbent position the patients swallow more air than when erect, and that in this position the passage of air down the intestine is not hindered by the "water-trap" at the pylorus as it is when the patient is erect. This is the reason one finds more flatus on the second post-operative day than on the first.

The author found the effect of pitressin was ideal in 13 out of 15 cases. In 3 of these cases it was necessary to administer the 10 units in a single dose, one-half hour before the examination in order to get the desired effect, which was obtained only upon a third examination. With the injection of 10 units of pitressin the patients complained of temporary but fairly marked gastric pain, and they became somewhat pale. Their pulse rate was not affected. Repeated observations have failed to show any marked rise in blood pressure. It is recognized that this is contrary to the reports from another source.

In spite of the inconvenience that a single dose of 10 units gives the patient, the author maintains that the advantages offered by his method justifies one giving it preference.

Investigations of the effect of pitressin on the colon after injection of the contrast enema shows no perceptible change in the position or dimentions of the colon. In the colon after being filled with residues from an opaque repast taken 24 hours before, the contrast substance after the injection of pitressin is seen to have been moved in an anal direction.

Special success has been found in gall bladder roentgenography, the intestinal gas being freed from the gall bladder

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region in the majority of cases. No contraction of the gall bladder was noted after the use of 10 units of pitressin given intramuscularly in one dose.

The study showed that with pitressin injection gas is far less likely to complicate the roentgen examination than without its administration.

James T. Case.

EMERY, E. S., JR.

The Use of Adsorbents in Gastro-Intestinal Disease. J. A. M. A., Vol. 108, p. 202, Jan. 19, 1937.

Adsorption may be defined as the attachment of one substance to the surface of another. Usually the substances are of a colloidal nature with large sized molecules. It is a complicated subject and the therapeutic action of them in the gastro-intestinal tract cannot always be predicted by the laboratory.

Clinically only charcoal and kaolin have been used because of their adsorptive properties. Charcoal has an excellent affinity for gases when dry, and will also adsorb various organic acids and drugs. Recently, activated charcoal, that is heated to a certain temperature, has been recommended because of a higher adsorptive capacity.

Kaolin, a mixture of aluminum silicate and other substances, has been used in China for centuries in the treatment of summer diarrheas and cholera. The action of kaolin is not exactly known, but Fautus believes that it changes the intestinal flora from a proteolytic to an aciduric one over a period of from ten to thirty days.

However, the use of these substances is limited because of their amphoteric qualities, because of the danger of forming plugs which may cause partial or complete bowel obstruction, or trauma to the intestinal wall.

Clinically, kaolin is indicated in patients suffering from severe food poisoning and dysentery. It is not indicated in those diarrheas due to nervousness, fat intolerance, exophthalmic goitre, pernicious anemia, or amebic dysentery. It seems that it is contraindicated in the treatment of idiapathic ulcerative colitis because the large amount necessary to produce results would interefer with adsorption in the rest of the tract. It is also contraindicated in diverticulitis, the dyspepsias and autointoxication.

Francis D. Murphy, Milwaukee.

JOHNSON, SYDNEY E.

The Frequency of Air Under the Diaphragm in Perforated Gastric and Duodenal Ulcer. J. A. M. A., 108:295, Jan. 23, 1937.

The finding of air under the diaphragm has long been known to be an important point in the diagnosis of perforated peptic ulcer. The exact frequency of the finding has not, however, been demonstrated. In an analysis of forty-two cases of proved perforated peptic ulcer the author found that thirty-five or eighty-three per cent showed roentgenographic evidence of pneumoperitoneum. He also found it was important to do the roentgen examination as early as possible especially where there is a problem of differential diagnosis.

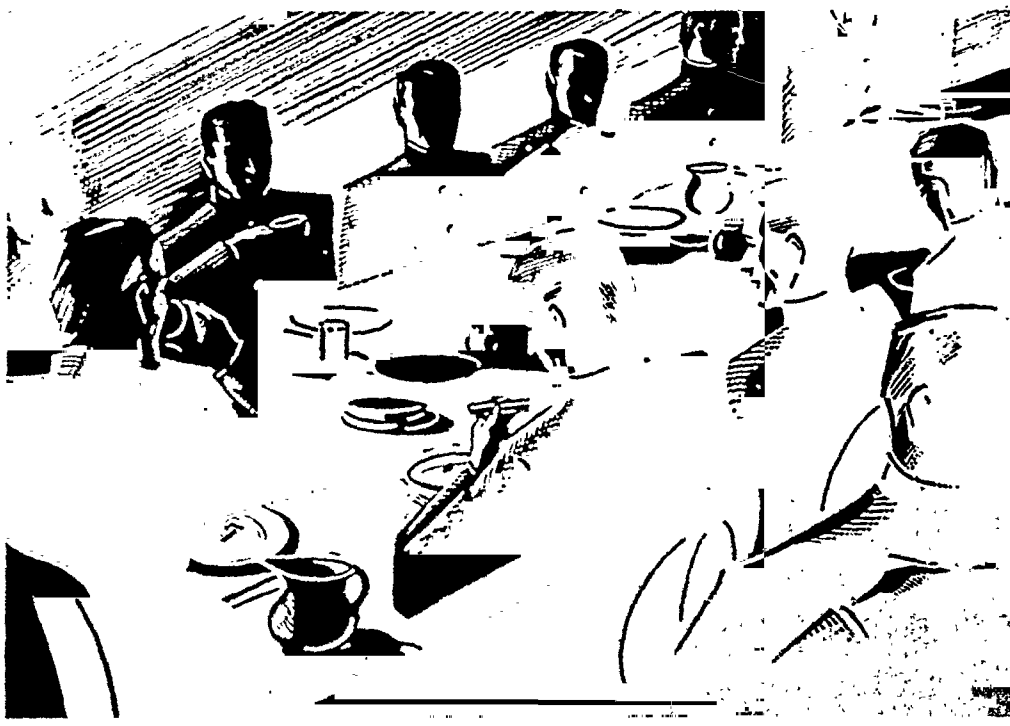
Francis D. Murphy, Milwaukee.

OCHSNER, ALTON AND STORK, AMBROSE H.

Mechanical Decompression of the Small Intestine in Ileus. J. A. M. A., 108:260, Jan. 23, 1937.

The "stripping" or "milking" out of the contents of the intestine in those cases where distention is so severe that replacement of the bowel within the abdominal cavity is very difficult has been used enthusiastically by some men; others are not in favor of it. The present report is an analysis by the author of sixteen clinical cases of intestinal obstruction operated on between the years 1928 to 1931, before the introduction of the Wangensteen method of drainage. After studying these cases the author believes that stripping of the intestine should seldom if ever be done. He has observed that postoperatively there is a fall in blood pressure, an impairment of intestinal





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activity and muscular tone. Even when done very carefully there is considerable trauma and shock resulting from the procedure, subserous hemorrhages being observed in some of the cases.

Proper preoperative preparation such as the replacement of electrolytes, administration of heat to the abdomen, liberal doses of morphine and the employment of an indwelling gastric catheter attached to a suction apparatus will in most cases relieve the distention. Even if these procedures do not relieve the distention the untoward effects following stripping are so severe that patients get along just as well without as with it.

Francis D. Murphy, Milwaukee.

HARKINS, H. N.

Mesenteric Vascular Occlusion of Arterial and of Venous Origin. Arch. of Path., 22:5, 637, Nov., 1936.

The author reviews the literature on abdominal vascular occlusion under four headings and analyzes nine cases mainly from the standpoint of "secondary shock" as the actual or contributing cause of death. "Secondary shock" is defined as the syndrome due to the loss of large amounts of plasma-like fluid or blood from the circulating blood stream. Clinically the occlusions were divided into four types: (1) thrombosis of the portal vein, due either to pylethrombophlebitis or to ordinary thrombosis; (2) occlusion of the mesenteric vein, usually due to thrombosis and often associated with thrombosis of the portal vein; (3) occlusion of the mesenteric artery, often embolic in origin, and (4) intestinal strangulation, in which often both veins and arteries are occluded.

Of the nine cases reported eight patients died and came to autopsy and one patient, a boy aged sixteen, lived after a resection of four feet of small intestine. Three cases were of the venous type and six were of arterial origin. Two of the latter cases presented no infarction of the intestine, explained on the assumption that a large collateral circulation existed in each. In the remaining six cases extensive hemorrhagic extravasation into the bowel occurred and much free fluid was found in the peritoneal cavity; so great a loss of circulating blood plasma that the author considered it an important, at least contributing, cause of death. Arterial occlusion was more frequent than venous. Most of the patients were in the upper middle age group and most of them had a pre-existing cardiovascular disease. In all an exaggerated symptom of pain, out of proportion to objective signs in the abdomen, was noted.

N. W. Jones, Portland.

LOEFFLER, L.

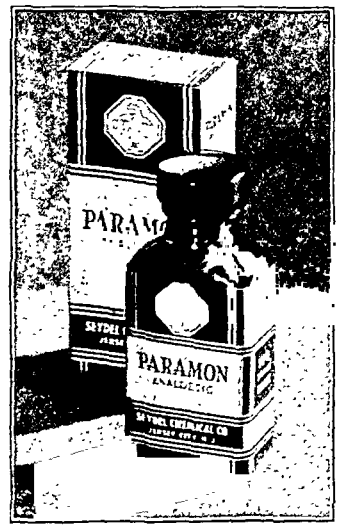
Genesis of Intestinal Infarction Following Embolization of the Superior Mesenteric Artery. Arch. of Path., 22:6, 755, Dec., 1936.

The author ligated the superior mesenteric artery and the portal vein in rats and studied their immediate effects under the microscope with low magnification in order to throw light, if possible, on the presence of hemorrhagic infarction of the small intestine after embolic occlusion of the superior mesenteric artery in man. The latter occurs, as evidenced by autopsy findings, whereas one would expect that occlusion of the artery would result in anemic necrosis of the gut.

The author found that if the animal lived a few hours after experimental ligation of the superior mesenteric artery simple anemic necrosis resulted. The gut became softened, contracted and empty, some imbibition took place, and small hemorrhages with congested capillaries were seen, but hemorrhagic infarction was not present. After ligation of the portal vein the intestine was dark red, suffused with numerous hemorrhages, was dilated and filled with bloody mucoid material. The ex-

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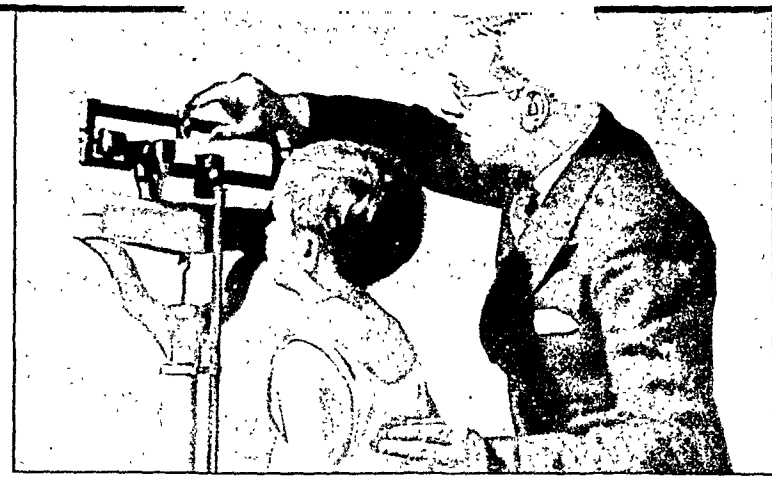
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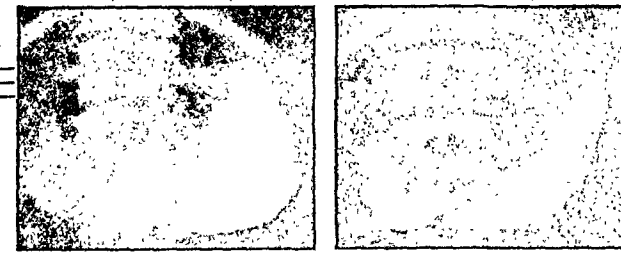
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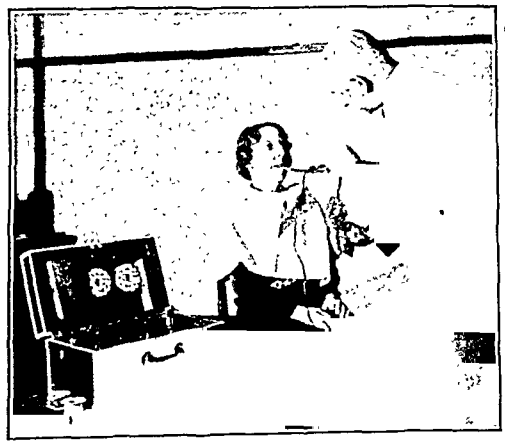


● *The x-ray reproductions show the stomach 2 hours after a starch meal was taken, without and with Ovaltine. The average decrease in gastric contents due to Ovaltine was 20%.*

periments supported his belief that collateral circulation was not responsible for the presence or absence of changes in the tissues unless such channels are present in "excessive" numbers. Microscopically, it was found in vivo that the cause of hemorrhagic infarction is neither venous reflux or arterial reflux nor collateral circulation. In man anemic necrosis of the bowel does not occur after embolism, but an infarction analagous to a pulmonary infarct occurs because circulation with which one deals in embolism is not a normal but a failing circulation which predisposes to stasis and hemorrhage. The cause of the hemorrhagic infarction is not to be sought in the region of the infarct but in the congested and altered state of the circulatory channels. It seems fundamental that there is a difference between the experimental results and the findings observed clinically; that this difference is due to markedly increased venous pressure and that this condition of passive congestion actually exists in the intestinal circulation at the time embolism occurs.

N. W. Jones, Portland.

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The use of the gastric camera is similar to the use of an ordinary stomach tube. The entire procedure takes less than a minute.

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ROSENKRANZ, K. AND HOWARD, L. D.

Tubular Tuberculosis of the Liver. Arch. of Path., 22:6, 743, Dec., 1936.

The authors present three typical cases of tuberculosis of the intrahepatic bile ducts, so-called tubular tuberculosis of the liver. Two occurred in young male Filipinos and one in a young white woman. All three suffered from generalized tuberculosis. The authors conclude that two factors are necessary for the origin and extension of tuberculous cholangeitis. The first is an early lymphatic and hematogenous generalized spread of the primary infection before resistance has been established. The second is an intestinal site for the primary infection and extensive caseation of the mesenteric glands. Caseous tubercles then develop in the periportal tissue and rupture into the bile ducts. The bile ducts themselves are not primarily infected. This type of tuberculosis is usually found in young children and in races that do not have high resistance against infection.

N. W. Jones, Portland.

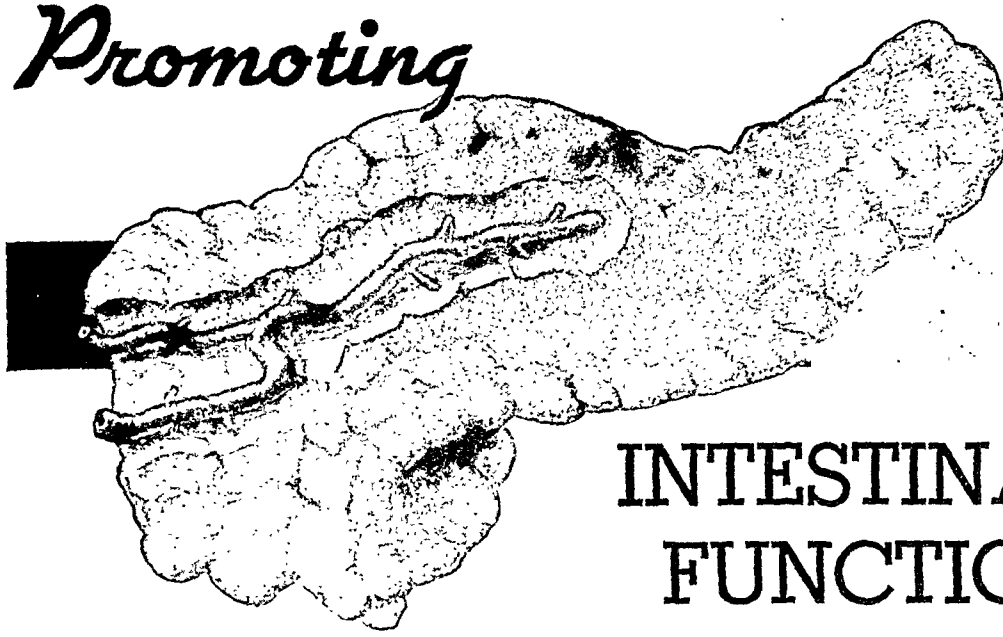
BRUES, A. M., DRURY, D. R. AND BRUES, M. C.

A Quantitative Study of Cell Growth in Regenerating Liver. Arch. of Path., 22:5, 658, Nov., 1936.

The author studied the rate of growth of liver tissue both as regards mass and the increase in cell number during the process of regeneration following partial hepatectomy in the albino rat. It had been shown previously by Adolph in case of cultures of paramecium that these two elements of growth varied independently of each other with variation of temperature.

Forty animals on a bread and milk diet were studied at different periods of time under as nearly controlled conditions as possible. Six animals were kept on a high carbohydrate diet for a week before operation, eleven on a high protein diet, thirteen on a high fat diet, and four were starved for four days previous to operation, at which time about 70 per cent of the liver was removed. The result of the study showed that the mass of the residual liver fragment increased over 50 per cent in the first twenty-four hours after operation and over 100 per cent in the first forty-eight hours. A secondary increase occurred after six days incident to the regaining of weight lost postoperatively. The number of cells in the fragment, however, showed no significant increase in the first twenty-four hours, but later they increased in number about as the mass increased, except that there was no secondary increase after several days. In starved animals mass increased less than in fed animals, but the cell number increase was about

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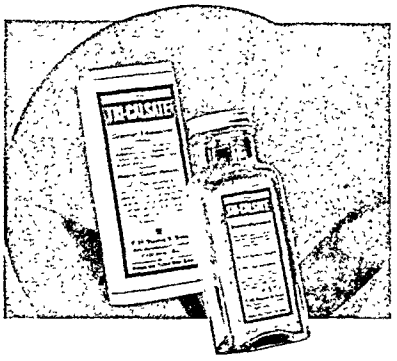
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the same. High carbohydrate and high protein diets showed less increase in liver mass than a normal diet, but the cell increase was not much affected. A high fat diet cut down the cell increase markedly, much more than did starvation. The normal nitrogen content of the fasting rat livers in the series was 3.5 per cent. The tissue added the first day contained 1.4 per cent. From then on the restored liver rapidly approached normal liver in nitrogen content.

In general it was found that the rate of restoration of liver tissue was markedly affected by diet, but the increase of cells in number was less dependent both on diet and on growth in mass of the tissue.

N. W. Jones, Portland.

FOUCAR, F. H.

Syphilis of the Gastro-Intestinal Tract. Report of a Case of Gumma of Transverse Colon with Review of the Literature. Amer. Jour. Path., XIII:1, 65, Jan., 1937.

A case of syphilis of the transverse colon in a male, aged 32 years, is reported, in which treponema pallida were demonstrated in the tissues. During life the patient had given repeated negative Wassermann blood reactions, but + to +++ Kahn tests. Insufficient antisyphilitic treatment had been administered. In March, 1934, his appendix was removed because of pain in the right lower abdomen. In October, 1936, he presented a movable tumor mass in the right abdomen and suffered colicky attacks of watery diarrhea without melena and dull abdominal pain with loss of weight and strength. A roentgen ray diagnosis of annular carcinoma of the transverse colon near the hepatic flexure was made.

Twelve cases of acquired syphilis of the intestine, including the author's are reviewed. Their ages averaged 44 years. Eight were males and 4 females. The Wassermann reaction was negative in one-half of the cases. The lesions were single in 8 and multiple in 4. The jejunum was involved 6 times, the ileum 2 and the large intestine 4 times. None of the cases were correctly diagnosed. Nine were diagnosed preoperatively as carcinoma, one as cholecystitis and one as intussusception. One patient died of generalized peritonitis following perforation of a syphilitic jejunal ulcer. Suggestive roentgen ray evidence of intestinal syphilis is that obstruction is usually in the small bowel and there may be multiple lesions present. When in the colon the lesion is more frequently away from the flexures, whereas carcinoma is apt to involve them.

N. W. Jones, Portland.

FOOT, N. C.

The Identification of Tumor Cells in Sediments of Serous Effusions. Am. Jour. Path., XIII:1, 1, Jan., 1937.

The diagnostic value of reported cells in a given fluid for examination the author summarizes in the following manner:

1. The presence of fragments of tumor with the cells arranged in acini or papillae about a stroma that is definitely fibrovascular is positive evidence of primary or metastatic malignant tumor of the serous membrane in question.

2. A nucleolar-nuclear ratio (n/N ratio) above 0.25 is of undoubted value; one of 0.30 or more practically pathognomonic of the presence of tumor.

3. Mesothelial covering cells are most easily confused with tumor cells on account of their large size and prominent nucleus, but they are uniform and regular in size. Tumor cells show a wide variation in measurements and have a high n/N ratio.

4. Multinucleation and cell clumping is of no diagnostic value. Mitoses occur in cells in both sediments, but monster or abnormal mitoses are found only in tumor cells.

5. The presence of erythrocytes and fibrin is of little diagnostic significance.

N. W. Jones, Portland.

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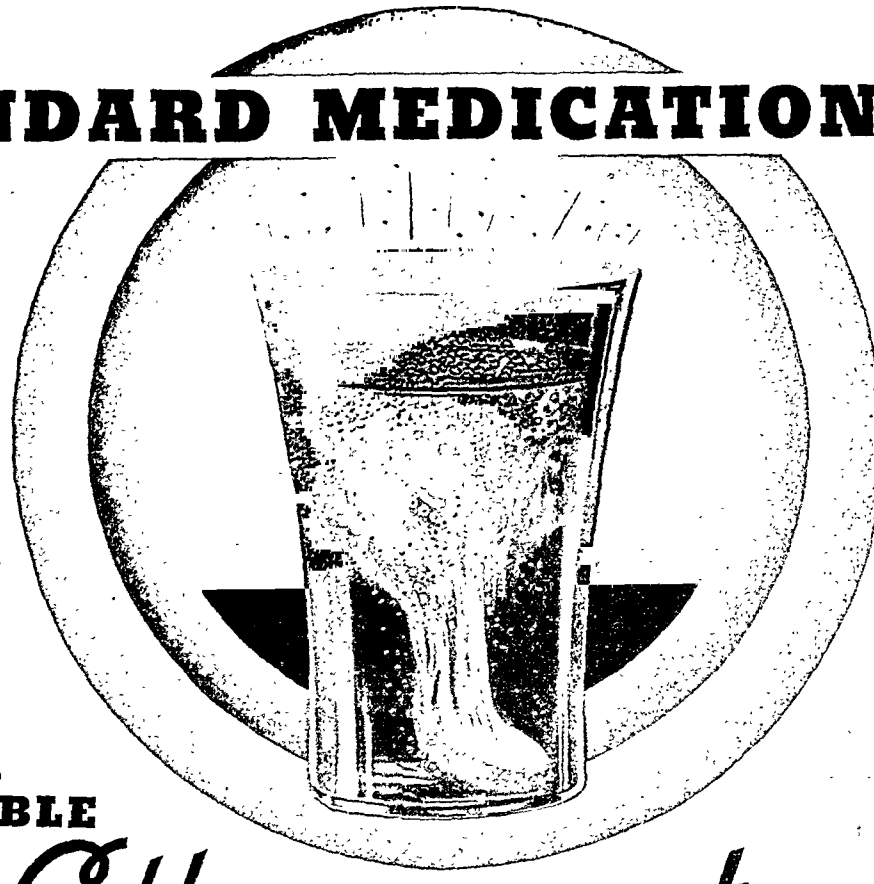
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VIENNA TO HAVE INTERNATIONAL CONGRESS OF SHORT WAVE SPECIALISTS. DOCTORS D'ARSONVAL AND ZENNECK, AND SENATOR MARCONI ON COMMITTEE OF JULY CONGRESS.

From July 12th to 17th the scientific workers in one of the most rapidly advancing fields of physics, chemistry, biology and medicine will convene in congress in Vienna under the patronage of official Austria as represented by a committee including the Federal President, the Austrian Chancellor, the Rector of the celebrated University of Vienna, the Rector of the Vienna Technical College and the Mayor of the City of Vienna. The Congress sessions will be comprised of lectures by world famous scientists followed by brief readings given by members and general discussions. The papers read by members must not take more than fifteen minutes reading time. Those wishing to read papers are requested to file a special application. The languages admitted are English, German, French and Italian. The major papers read, as well as those presented by members will be printed in full and copies distributed to those attending the Congress provided applications are received in time. In conjunction with the Congress an exhibit showing the latest advances in the short wave field, both in the abstract field and the field of applied practice will remain open throughout the congress.

The subjects to be dealt with include: Physics, Biology, Chemistry and Medicine. In the field of Physics the subjects to be covered are: the properties of short waves and ultra short waves; generation, conduction, radiation and propagation; reflection refraction, absorption; measurement of SW and USW. Exploration of Heaviside-Appleton layers of the atmosphere. Chemistry and Physical Chemistry will be thoroughly explored in its relation to short wave work and the practical aspects of short wave application in the physical field will be treated extensively.

In Biology the action of short waves of various types on plants, animals, organisms, enzymes and ferments; heat effect and size particles; percutaneous SW diathermy; destruction of noxious insects; experiments will be included.

In the medical field, the connection of which with short wave therapy has aroused wide world interest, the following topics will receive attention: indications and counter indications for the therapeutical application of SW and USW. USW therapy, its application in cases of acute inflammations of bacterial genesis in internal medicine, surgery, gynecology, dermatology, opthalmology, otiatry and neurology; SW therapy in connection with acute infectious diseases, especially with polomyelitis acuta; sensibilization by SW of malign neoplasms refractory to X-rays; SW diathermy, its application in cases of chronic rheumatic diseases of joints and muscles; the technical side of apparatus.

All lectures and discussions will take place in the morning, leaving the afternoons free for demonstrations, experimental work or sight seeing tours. Membership fee of the congress is thirty Austrian Schillings which fee includes the cost of all printed reports. The fee is payable in the local currency to the official Austrian representatives abroad. A crowded calendar of social events including official receptions and merry excursions has been planned to supplement the serious work of the members of the congress.

Programs and application blanks will be furnished upon request by writing to Austrian State Tourist Department, 630 Fifth Ave., New York City.

The two following abstracts throw light on the vitamin value of canned foods:*

SEBRELL, W. H., WHEELER, G. A. AND HUNT, D. J.

The Blacktongue-Preventive Value of Seven Foodstuffs. U. S. Public Health Reports, 50, 1333, 1935.

These investigators consider canine blacktongue and human pellagra to be analogous conditions, hence the determination of the blacktongue-preventive value of a food is considered a measure of its pellagra-preventive value.

Forty per cent of the total calories in an otherwise blacktongue producing diet were supplied by a commercial brand of canned chicken. Four dogs were kept for a year on this diet without the appearance of any symptoms of blacktongue, indicating that commercially canned chicken is a valuable source of the pellagra-preventive factor.

GOLDBERGER, JOSEPH, WHEELER, G. A. AND ROGERS, L. M.

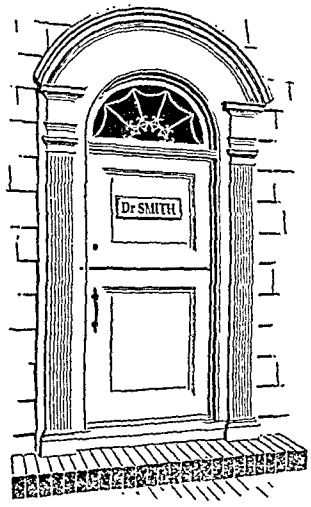
A Study of the Blacktongue-Preventive Value of Lard, Salt Pork, Dried Green Peas, and Canned Haddock. U. S. Public Health Reports, 45, 1297, 1930.

Blacktongue in dogs and pellagra in the human are analogous conditions, in the opinion of the authors; and the success or failure of a diet in preventing blacktongue is a satisfactory basis for the evaluation of its pellagra-preventive values.

Canned haddock, a moderately priced canned food, fed as a relatively large proportion of the diet, prevented the appearance of blacktongue in dogs. Canned haddock might well be included in the diet for the control or prevention of pellagra in rural areas of the South.

*These abstracts were furnished by the Research Department of the American Can Company. *Editor.*

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A tablespoon of Karo gives twice the number of calories (60) in comparison with a tablespoon of any powdered maltose-dextrins-dextrose, including Karo powdered. Karo is well tolerated, highly digestible, not readily fermentable and effectively utilized by infants.

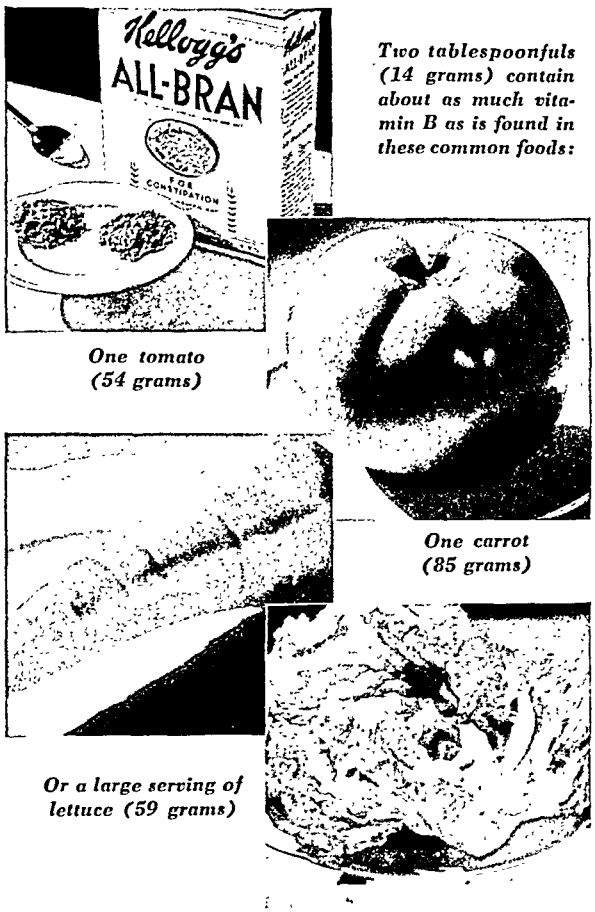
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Or a large serving of lettuce (59 grams)

NUTRITIONAL authorities recognize the importance of vitamin B in helping to maintain muscular tone in the intestines.

Kellogg's ALL-BRAN contributes a fair share of the vitamin B needed daily. This cereal also supplies iron for the blood and corrective "bulk." Within the body, ALL-BRAN absorbs twice its weight in water, and cleanses the system.

This natural laxative food may be served as a cereal with milk or cream, or cooked into recipes. Sold by all grocers. Made by Kellogg in Battle Creek.

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"We call attention to the direct-mail campaign of The Wander Company. This consists of a series of mailings of four-page pamphlets describing the results of research on Ovaltine. The first of this series deals with the effect of Ovaltine on the digestion of starches and the influence which this property exerts on gastric emptying time. The tone of the bulletin is dignified and conservative both in typography and copy. This type of promotion should be well received by the profession.

Fifth International Congress of Radiology to convene in Washington, D. C.

One of the most outstanding scientific events ever held in the United States has been set for Chicago this September, when the Fifth International Congress of Radiology convenes. It will be the first time that the world leaders in the medical and scientific development field of X-ray and radium have met in America, according to Dr. Arthur C. Christie, Washington, D. C., president of the Congress. The dates are September 13 to 17, inclusive, and the meeting place is the Palmer House.

At least 500 distinguished delegates and guests from a score of European countries as well as physicians from Mexico, Canada and Central and South America are expected to attend, with more than 2,000 other delegates and visitors from all parts of the United States.

The annual medical conventions of the leading radiological bodies of this country will be merged with the international congress. These include the American Roentgen society, the American College of Radiology, the Radiological Society of North America and the American Radium society.

The first International Congress of Radiology convened in London in 1925. Meetings are held every three years. The physicians and physicists met in Stockholm in 1928, in Paris in 1931 (where they paid tribute to the then living Madame Curie, co-discoverer of radium) and in Zurich in 1934.

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In affiliation with COOK COUNTY HOSPITAL

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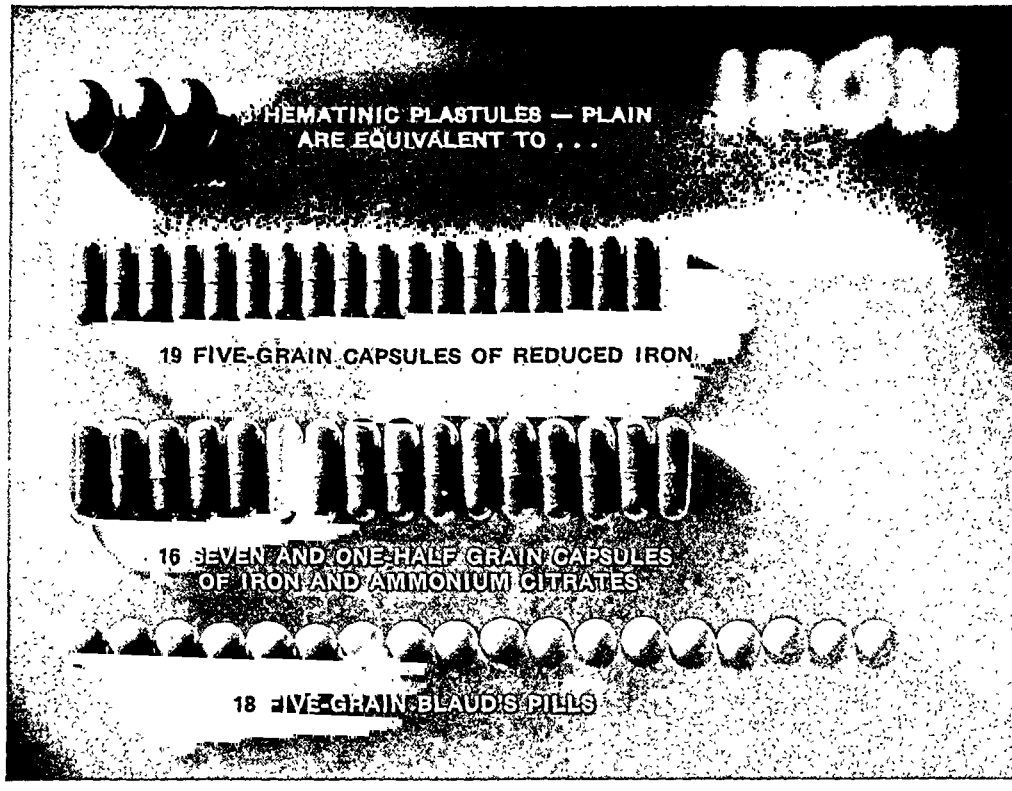
By Professor Rudolf Schindler

The course will consist of practical work in the use of the flexible gastroscope designed by Dr. Schindler, formerly of Munich, Germany. Gastroscopic examinations will be made daily, and during the second week gastroscopies will be carried out by each student. The clinical, x-ray and gastroscopic findings will be compared.

The course will occupy two hours daily from Monday to Friday for two weeks. Courses are offered on July 5-17 and August 2-14. Minimum attendance 2—Maximum attendance 4.

From July 19th to July 31st, Dr. Aaron Arkin and Dr. Rudolf Schindler will offer a forty hour course in Gastro-Enterology and Gastroscopy.

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Leaders in other branches of medicine will participate in the Congress too as Dr. Christie points out that "The Unity of Medicine" will be the theme of the entire Congress.

"These international congresses seek to maintain a continuity of program over the years, and in consequence such vital subjects to the radiologist (and to the general public) as diagnosis and treatment of cancer and many other diseases and teaching and training in radiology will be on the agenda of this congress as well as at former meetings.

"Radiology is an important branch of medicine, and is indeed part of the entire tree, and not merely a specialty as it was once regarded," added Dr. Christie.

More than 250 scientific papers will be read at the five-day meeting. These will be delivered in each lecturer's own language and will be automatically flashed on screens in English, German and French as the papers are read.

What will probably be the greatest scientific and technical exhibit in the history of a radiological congress will be assembled by physicians, physicists and manufacturers of such equipment in conjunction with the congress.

The general secretary of the congress, Dr. Benjamin H. Orndoff, is in charge of headquarters at 2561 North Clark street, Chicago, Ill. Honorary vice-presidents are Dr. George E. Pfahler of Philadelphia, Dr. James Ewing of New York and Dr. William D. Coolidge of Schenectady, N. Y. On the International Executive Committee are Dr. Arthur C. Christie of Washington, D. C., chairman; Dr. C. Thurstan Holland of Liverpool, Dr. Gosta Forssell of Stockholm, Dr. Antoine Beclere of Paris, Dr. Hans R. Schinz of Zurich, Dr. Karl Frik of Berlin, Dr. Mario Ponzio of Turin, Italy; Dr. Tamotsu Watanabe of Osaka, Japan; Dr. Heliodoro Tellez-Plasencia of Santander, Spain, and Dr. Gottwald Schwarz of Vienna.

From: Secretary's Office, International Congress, 2561 N. Clark Street, Chicago, Ill., U. S. A.

"CONNOTATIONS"

By
H. J. SIMMS, M.D.
DENVER, COLORADO

The occurrence of more than one gall bladder in the human body was probably first described in medical literature by Plasius, in 1674. Pliny makes mention that on the day of Emperor Augustus' naval victory at Actium (31 B. C.), a double gall bladder was found in the sacrificial victim.

Galen (131-201 A. D.) believed the function of the pancreas was to act as a cushion for the stomach. Malpighi (1628-1694) described the structure of this organ. The histology was not described until 1869, and then by Langerhans. Its main duct was recognized by Wirsung in 1642.

The relation of the pancreatic juice to digestion was first noted by Bernard, in 1856. Corvisart, in 1857, and Kuhne, in 1867, observed the effect of the pancreatic juice on carbohydrates, fats, and proteins.

A cervical rib was first described by Humauld, in 1742, and Coote, in 1861, resected such a rib.

Kuster, in 1883, first recommended the ideal operation of cystotomy. McRidity in America one year later advocated the same procedure.

Gelatinized Milk

SCORES IN

INFANT FEEDING TESTS

A preliminary study conducted in the Department of Pediatrics of a prominent Eastern University was made with three groups of infants (fifty babies in each). The study was intended to duplicate the usual type case as seen by the practicing physician such as vomiting, constipation, and other disorders relating to the digestive system.

To determine any differences between cow's milk, lactic acid milk, and gelatinized milk* was the purpose. The results as reported (Archives of Pediatrics January-February 1937) are:

1. Infants fed gelatinized milk appeared to be less susceptible to infections, especially upper respiratory infections, than those fed acidified or cow's milk.
2. The occurrence of diarrhea was less frequent in the gelatinized milk group and acidified milk group than in the plain milk group.
3. The group of infants fed gelatinized milk had a better rate of gain than those groups fed acidified milk or plain cow's milk.
4. Vomiting and "appetite poor" symptoms among the infants were obviated or showed improvements when fed gelatinized milk in contrast to the feeding results of the other groups which showed little change.
5. The infants in the gelatinized milk group had more favorable results than the acidified milk group or cow's milk group in relation to constipation.

* One or two per cent of Knox Gelatine was added to the formula water which had been boiled and cooled. The gelatine was softened ten minutes before being added to the milk of the formula.



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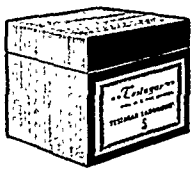
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*Am. J. Roentgen. 19.341, 1928. Am. J. Med. Scien. 6-182, 1931.
**Arch. Int. Med. 38 647, 1926. Am. J. Surg. 7:455, 1929.
***Am. J. Med. 6-1465. 1933. J. Lab. & Clin. Med. 19.567, 1934.

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Sampson, in 1725, recognized the distinction between obstructive and hemolytic jaundice.

Cholesterol gall stones are peculiar to man, however, biliary concretions known as ambergris occur in whales. These calculi are composed chiefly of cholesterol and are said to weigh as much as one hundred pounds.

Eller, in 1764, believed ganglia or synovial cysts resulted from rupture of the tendon sheath and extravasation of the synovial fluid into the tissues. Further opinion was suppressed until Gasselin, in 1852, suggested they developed from crypts in the synovial membrane.

Casper, in 1850, first mentioned the possibility of death from the delayed action of chloroform.

Nothnagel, in 1866, produced evidence that chloroform might produce fatty changes in the liver, heart and kidneys. Rosenbaum, in 1882, showed the liver to be poor in glycogen following administration of chloroform.

Fidel Pages, a young Spanish surgeon, perfected the technique of epidural anesthesia. He died from pneumonia a few days before his article appeared in literature. Dogliotti, in 1931, described the same technique before the Italian Surgical Congress though unaware of Pages previous report.

Congenital idiopathic cysts of the common bile duct was recognized by Vater, in 1723.

The first authentic case of gall bladder disease in a child was published by Gibson in 1722.

Von Neusser, in 1908, commented on the necessity of differentiation between pain of cardiac origin from the syndrome of pulmonary embolization. Hamburger and Saphir and more recently Averbuch have confirmed at autopsy that death presumably from coronary thrombosis is often due to pulmonary emboli.

Trendelenburg early observed the posture which he described was not free from circulatory embarassment during operative procedures. He advised against this position in plethoric individuals.

Cholesterol was first isolated by Conradi in 1775. It was analyzed by Chaureul in 1815. Flint, in 1862, believed the liver removed cholesterol from the blood and that hypercholesteremia depended upon pathologic changes in the liver.

Laborde, in 1874, injected irritants into the gall bladder of animals to determine whether painful stimuli were transmitted through the splanchnics.

Slipping ribs or recurring luxation of the lower costal cartilages with its associated symptoms was first described by Davis-Colley in 1922.

The first case of intestinal obstruction was recorded by Bartholin in 1654.

The first record to induce intravenous anesthesia was attempted by Ore in 1872. He used a solution of Chloral hydrate.

As far back as 1667 Hooke experimentally proved that the essential feature of respiration was the blood changes in the lungs.

The deformity now known as Dupuytren's contraction was described by Plater in 1610. Henry Clive, in 1808, included this abnormality among his surgical lectures. Dupuytren's classical description appeared in 1831.

The first case of torsion of the omentum was presented by Marchette in 1852. Twenty-nine years later Oberst gave a detailed description of this condition.

Modern literature attributes to recent investigators the recognition of regeneration of the liver after partial resection. Podwyssozki, in 1886, and Ponfick, in 1896, observed regenerative changes in the liver of rats, cats, guinea pigs, and rabbits. Both noted taat loss of liver substances was repaired by proliferation of liver cells.

VITAMIN REQUIREMENTS OF MAN

IV. VITAMIN B_1

● The multiple nature of vitamin B has been definitely established by intensive research within the past decade. Considerable quantitative information is now available concerning the requirements of certain species of animals for the various factors contained in the vitamin B complex. At the present time, however, the anti-neuritic vitamin B_1 is the only one of these factors for which the minimum requirement for man can be postulated.

Beriberi-preventing diets of Chinese coolies and natives of Java have been estimated to contain 200 International units of vitamin B_1 (1). Practical use is made of knowledge such as this in the Philippines, where the Bureau of Science, in a successful effort to combat beriberi, dispenses tikitiki (vitamin B_1 concentrate from rice polishings) containing approximately 200 International units of vitamin B_1 per daily dose.

It is generally agreed that the absolute requirement for this factor may be variable, depending upon such factors as size and caloric intake of the individual. However, equations have been derived which take into consideration some of these variables and are useful in estimating the adult vitamin B_1 requirement (2).

Application of these equations indicate that approximately 225 International units of vitamin B_1 per day are required for the average American adult. The average daily infant requirement has been estimated to be 50 International units, increasing to 200 units at the time of adolescence (1). The League of Nations Technical Commission recommends a daily intake of over 150 International units for pregnant and lactating women (3).

While it may be possible to estimate the daily intake of vitamin B_1 which will prevent clinical beriberi, it is not yet possible to state the minimum amount of the vitamin which, when imposed on an otherwise adequate diet, will promote optimum nutrition. There is increasing belief that some of the vague disorders, noted clinically, may be in reality manifestations of suboptimal vitamin B_1 intake (4).

Today, we have the new concept of nutrition which recommends the intelligent inclusion in the varied dietary regime of foods with known nutritive values—thereby insuring that the individual is not dwelling in "the twilight zone of nutrition". Thus has arisen the concept of "protective foods".

Results of formal bio-assay have established many commercially canned foods as valuable sources of vitamin B_1 (5).

Incorporation in the diet of the wide variety of foods—made available throughout the year by commercial canning—will assist in the acquisition of an adequate supply of vitamin B_1, as well as other members of the B complex, essential to human nutrition and usually occurring in nature along with the antineuritic factor (6).

AMERICAN CAN COMPANY

230 Park Avenue, New York City

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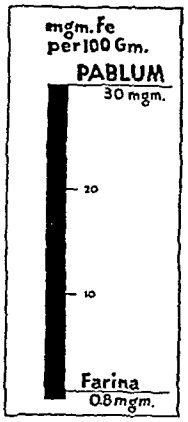
This is the twenty-fifth in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.



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For bland diet therapy, especially ULCER cases—PABLUM

FAR too often the bland diet prescribed for gastric ulcer, colitis, and similar gastro-intestinal disorders is a deficient diet. An analysis made by Troutt of ulcer diets used by 6 leading hospitals in different sections of the country showed them to be "well below the Sherman standard of 15 milligrams" in iron and low in the water-soluble vitamins.[1] "Vitamin B would appear to be represented at a maintenance level in most cases," writes Troutt, "but the possible relation of vitamin B to gastro-intestinal function and appetite should make one pause before accepting a low standard."



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Low in Fiber—High in Iron

Pablum is the *only food rich in a wide variety of the accessory food factors that can be fed over long periods of time without danger of gastro-intestinal irritation.* Its fiber content is only 0.9%. Yet Pablum contains 37 times more iron than farina and is an excellent source (+ + +) of vitamins B and G, in which farina is deficient. Supplying 8½ mgms. iron per ounce, Pablum is 8 times richer than spinach in iron.

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The high vitamin B content of Pablum assumes new importance in light of recent laboratory studies showing that avitaminosis B predisposes to certain gastro-intestinal disorders. Apropos of this, Cowgill says, "Gastric ulcer is another disorder which can conceivably be related to vitamin B deficiency. Insofar as the treatment of this condition usually involves a marked restriction of diet the occurrence of at least a moderate shortage of this vitamin is by no means unlikely."[2]

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many *varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a* double boiler (studies *in vitro* by Ross and Burrill[3]). In addition to the above advantages, Pablum is the only base-forming cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum (Mead's Cereal thoroughly cooked) consists of wheatmeal, oatmeal, cornmeal, wheat embyro, alfalfa, yeast, beef bone, iron salt and sodium chloride. [1-3] Bibliography on request.

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The Treatment of Amebic Colitis with Diiodohydroxylquinoline (Diodoquin)*

By

DANIEL N. SILVERMAN, M.D., F.A.C.P.†

NEW ORLEANS, LOUISIANA

DURING the past ten months, from June, 1936, to April, 1937, a certain number of cases of amebic colitis have been chosen for treatment with a new drug, diiodohydroxylquinoline, represented to the trade as Diodoquin. Up to the time of this investigation this preparation had not been used in a sufficient number of cases to establish the correct dosage or to evaluate its general amebicidal value in amebic infection of the bowel. The daily dosage required to control the disease without deleterious effects and the number of days necessary for such dosage had not definitely been determined. Similar drugs to the one being reported upon in this communication have been used with encouraging results. Their similarity to Diodoquin is based upon the iodine constituent of the oxyquinolines, some of which contain sulphur. Diodoquin differs from the others in the amount of iodine in the compound. The former contains not less than 63.9% of iodine while the other preparations on the market contain about 50% less of this element.

This additional proportion of iodine has not given any deleterious reaction, in fact no appreciable toxic symptoms have manifested themselves. These observations were brought out in view of the administration of twice the daily dosage recommended by the manufacturer. The larger quantity was utilized in several instances because of the severity of the infection, the extensive pathology observed in the lower colon, accompanied by intense focal and systemic reactions. In such persons the larger doses were tried in order to increase the concentration of the drug in the intestinal tract and thereby inhibit the action of the amebae.

As stated above, reports on the treatment of amebic colitis with this new preparation, diiodohydroxylquinoline, are very meagre. Only mention has been made by some observers of the employment of this drug for the condition in question. For example, Tenny speaks of the encouraging results obtained in a clinical way and that he is exhibiting it in suspicious cases of a chronic low grade ameboid infection. This writer believes Diodoquin meets the requirements of an amebicide free from toxicity and practical for routine use in the treatment of active cases. Tenny does not give any definite information on the number of cases he treated, the types of cases, the dosage of the drug, or on the very important criterion of permanent results, namely, repeated negative examinations of the stools for the ameba.

In a recent article entitled "The Management of Chronic Relapsing Amebiasis," Hummel (2) gives an analysis of his 123 such cases. In one patient only he treated the amebic infection with the new preparation. He emphasizes the increased amebicidal action of diiodohydroxylquinoline because this preparation has the additional action of an atom of iodine in the molecule. Trophozoites and cysts disappeared from the stool in five days. However, recurrences were frequent, and, Hummel reiterates the prospects of cure are remote with any of our present means of treatment once the case has become chronic.

Craig (3), has treated 8 carriers (chronic amebic colitis) with disappearance of the parasites from the stools. His subjects were free of symptoms when treatment was instituted.

In the present report the author has the opportunity to discuss the analysis of 25 cases of amebic colitis treated with this drug. Among these twenty-five patients were nine acute fulminating cases. Their histories were of sudden onset from a few days to two weeks before consulting a physician. Since there were no other cases of acute amebic dysentery similar to mine in the reports of other writers that had made use of Diodoquin, the author was afforded an initial opportunity of observing the effects of this drug on acute amebic colitis, as evidenced by the changes in the living pathology presented in the rectum and sigmoid through the sigmoidoscope. The dosage of the preparation as herein established is much larger than previously recommended. The daily dosage employed in this series of patients has proven non-toxic and of maximum therapeutic value. The quantity heretofore recommended has been from 7.5 to 15 grains every 24 hours, but the author has established a daily dosage of 22.5 to 30 grains without observing any toxic effects or untoward results.

In the 16 chronic cases, there were only two with diarrheal symptoms. The other 14 had varied complaints, particularly abdominal distress comprising upper and lower abdominal pain, indigestion, headaches, malaise and weakness. In this connection we must not overlook the always present possibility that amebic colitis exists in every case of undiagnosed abdominal condition.

As an example of acute fulminating dysentery caused by Endamoeba histolytica and showing the satisfactory results of treatment with sufficient dosage of Diodoquin, the following case is described:

M. H., white male, age 50, was admitted to the hospital on February 2, 1937, complaining of severe griping sensations in the abdomen, malaise and frequent bloody mucus stools of one week's duration. On palpation of the rectum, a hard, irregular mass, suggesting possible carcinoma was detected. The proctoscopic examination showed this mass to be ulcerated and necrotic with numerous ulcers in the rectum and sigmoid. Trophozoites of Endamoeba histolytica were found in large numbers. On February 6, treatment was started with 10 grains of Diodoquin three times daily. February 10th, palpation of the rectum failed to reveal any evidence of the previous tumor formation. Inspection showed some granulation of the mucous membrane with puckering of a few ulcers. February 13th, ulcers were still visible and the stools contained cysts of

*The material used in this investigation was furnished by G. D. Searle & Co.

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Submitted April 7, 1937.

the ameba. February 15th, after 9 days of treatment, with a total dosage of 270 grains of Diodoquin, the patient was symptom free. Treatment was continued and on February 19th the rectum still showed one large ulcer with granulation tissue in its area. February 21st no amebae were found in the stool. February 25th, 19 days after instituting treatment, all evidence of rectal and sigmoid pathology had disappeared and the drug was discontinued. Up to the present writing, April 5th, the stools, obtained at weekly intervals, after saline purges, have not shown any amebae.

An example of *severe amebic dysentery* in which treatment with Diodoquin was begun two weeks after the onset of intense diarrhea with muco-sanguinous stools, was Dr. R. Q., who showed extensive ulceration of the rectum and sigmoid with numerous trophozoites of the ameba on January 2, 1937. He was given 7.5 grains of Diodoquin three times daily and on January 11 no ulcers were seen in the rectum or sigmoid on proctoscopy. Upon January 12th, cysts were found in the stool but on January 14th no trophozoites or cysts were recoverable. Treatment was discontinued on January 16th. Repeated examinations of the saline-purged stools fail to reveal any Endamoeba histolytica at the present writing, April 5, 1937.

The chronic cases of amebic colitis, 16 in number, were administered 9 tablets of Diodoquin per day, for an average of 16 days. Fifteen of these patients have been free of symptoms for periods ranging from one month to eight months. They have shown no recurrence of amebae in the stools. One patient continues to have diarrhea of a watery nature because of an associated flagellosis although no amebae have recurred.

SUMMARY

In a preliminary study of 25 cases of acute and chronic amebic colitis treated with a newer oxyquinoline compound of iodine containing approximately 64% of iodine, beneficial results were obtained in a comparatively short period of drug administration. These results have been observed over varying lengths of time, from one to nine months. The benefits were measured by the effects, in acute cases, on the pathology in the rectum and sigmoid as determined by repeated sigmoidoscopic examination before, during and following treatment. Results were determined in both acute and chronic cases of amebic colitis by microscopic study of saline-purged stools at regular intervals of one week. Invariably the amebae disappeared from the stool following sixteen days of treatment. The writer finds that the dosage of diiodohydroxylquinoline should be 22.5 grains to 30 grains per day. The drug is practically non-toxic, with headache being one predominant symptom in the three patients that complained.

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A Complement Fixation Test for Amebiasis with an Increased Antibody Content*

By

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and

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CHICAGO, ILLINOIS

DURING the last few years it was observed that infections with ameba histolytica are of more frequent occurrence than was previously anticipated. The difficulties of diagnosing this infection at an early stage are manifold. A number of intestinal disorders resemble amebiasis very closely and frequently the final diagnosis rests entirely with the laboratory tests. The conditions for examination of fresh and stained fecal smears are not always satisfactory although the clinical findings indicate amebiasis. Similar experiences are encountered with amebic cultures. In addition the number of reliable laboratory workers, capable of diagnosing amebae in fresh smears or preparing satisfactory cultures is relatively small. In the early stage of its development, the complement fixation test for amebiasis was considered only as a secondary test to confirm other laboratory tests or clinical findings (7, 8, 10, 11, 15). The lack of appreciation of the complement fixation test for diagnostic purposes was due to its relatively low percentage of positiveness in established amebic infections. The low percentage of positiveness was caused mainly by the weak antigen and the relatively small amount of antibodies used in the test. Several attempts were made to improve the antigen (6, 9, 12, 17, 18, 21), but no one seems to have tried to utilize the antibodies in a more satisfactory manner. Weiss and Arnold (21, 22), introduced several innovations in the ameba complement fixation test. They prepared a stronger antigen, and simplified the antigen titration. The improved antigen could be used in much smaller amounts, thus avoiding hemolysis caused by the presence of a relatively large amount of alcohol in the extract. They also showed that if large amounts of serum (1 c.c. instead of 0.1 c.c.) were used in the test, the additional antibodies were fixed, in fact the stability of the procedure increases proportionately. In addition they used as a positive control a rabbit serum prepared with ameba cultures or alcoholic extracts from amebae. The use of the rabbit immune serum instead of a positive serum offers the advantage, that it is surely positive and aways available as a control. These improvements resulted in a higher percentage of positiveness, without

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Submitted April 8, 1937.

increasing the number of nonspecific positive reactions.

The great interest evoked by this test and the possibility of increasing the sensitiveness of this procedure led to additional studies. As the outcome of these experiments an improved procedure was developed which is described below.

TABLE I

The influence of natural amboceptor on the complement fixation test for amebiasis

Number and kind of sera	Reaction	½ Units of Immune Serum Amboceptor Without	With
42	Hemolysis	—	41
Normal	Slight hemolysis	—	1
	No hemolysis	42	—
56	Hemolysis	—	49
Syphilitic	Slight hemolysis	—	1
	No hemolysis	54	1
72	Hemolysis	—	4
Amebic	Slight hemolysis	—	10
	No hemolysis	72	58

EXPERIMENTS

I. *The content in natural amboceptor of normal, syphilitic and amebic sera.*

The employment of larger amounts of serum in the complement fixation test necessitates a closer study of the natural amboceptor in various sera. It has been known for a considerable length of time, that every human serum contains a natural amboceptor for sheep cells in some quantity and that the amount varies in every serum. By using larger amounts of serum in the fixation test, the amount of natural amboceptor increases correspondingly. It appeared therefore, worth-while to investigate the amount of amboceptor in various sera and to determine to what extent this natural amboceptor may interfere with the outcome of results in the complement fixation test.

Forty-two normal, fifty-one syphilitic and seventy-two amebic sera were inactivated for one hour at 55-56° C. and then complement fixation tests for amebiasis were performed, in one series without amboceptor and in the other series with five units of amboceptor. The results are given in Table I. It is evident, that natural amboceptor has little influence on the outcome of the fixation if the immune serum-amboceptor and the blood cells in the hemolytic system are used in sufficient quantities.

II. *Comparative studies of the complement fixation test for amebiasis with increasing amounts of serum.*

One hundred and eighty-one sera of various stages of amebiasis, three hundred and ten syphilitic sera and four hundred and twenty-four sera of various other diseases were included in this study. Only sera of patients were studied in which the diagnosis had been well established by other laboratory methods and clinical findings. The detailed results are given in Table II. The advantage of using larger amounts of serum is plainly noticeable in every stage of amebiasis. The increase of non-specific positive reactions is rather small and amounts to less than one per cent.

THE TEST

Apparatus and glassware: Pipettes, tubes and other glassware are the same as is used in any other complement fixation test. Both incubator and water bath easily adjustable to 37° C., and varying not more than between 36°-38° C. are satisfactory. In the proposed procedure the reagents are used in a higher concentration than in most complement fixation tests. It is therefore essential that the tubes be vigorously shaken to insure a uniform mixture of added reagents. For this reason the use of shaking machine preceding both incubations appears advisable.

Antigen preparation: The liquid contents of a forty-eight to seventy-two hour culture of endameba histolytica grown on any of the satisfactory media (2, 3, 4, 5, 13, 14, 19) are poured in centrifuge tubes and centrifuged for fifteen minutes at high speed. The supernatant fluid is then removed and the sediment is transferred to wide glass

TABLE II

Complement fixation test for amebiasis with increasing amounts of serum. All acute, chronic and carrier cases had positive feces

		Results of the Complement Fixation Test for Amebiasis Using Inactivated Serum											
		0.1 c.c.				1.0 c.c.				2.0 c.c.			
		+ + + +	+ + +	+ or ±	—	+ + + +	+ + +	+ or ±	—	+ + + +	+ + —	+ or ±	—
Acute Amebiasis Total Cases 49	Number Cases	14	9	6	20	21	11	7	10	32	7	1	6
Chronic Amebiasis Total Cases 62	Number Cases	23	11	10	15	34	15	5	8	40	16	3	3
Amebic Carriers Total Cases 70	Number Cases	33	17	5	17	44	12	4	10	53	8	7	2
Wassermann Positive Sera Total Cases 310 (Syphilis)	Number Cases	5	2	0	303	5	2	1	302	6	2	1	301
Wassermann Negative Sera Total Cases 424 (Other Diseases)	Number Cases	0	2	0	422	0	3	1	420	1	3	1	419

dishes, covered with a small amount of acetone and allowed to dry at 37° C. The dry residue is scraped off with a sharp knife and the powder extracted with absolute alcohol in the ratio of 1:20 for two weeks at 55° C. in a water bath. The extract gradually assumes, a distinct yellow color. The fluid is then removed by filtration through paper or by centrifuging from the sediment. The extract is then ready for antigen titration. If the subsequent titration shows a weak extract, this can be corrected by concentration of the antigen through evaporation at 37° C. to the desired strength. If the antigen is too strong, it can be satisfactorily adjusted by diluting it with a sufficient quantity of absolute alcohol. The completed antigen should be kept at room temperature in a tightly stoppered bottle in order to avoid evaporation of the alcohol. Rubber stoppers are preferred to ordinary corks.

Titration of the antigen: Twenty Wassermann tubes are placed in two rows of a rack. Increasing amounts of the extract, 0.05, 0.1, 0.2, 0.3 c.c. diluted 1:10; 0.2, 0.25, 0.3 c.c. diluted 1:5; 0.2, 0.25, 0.3 diluted 1:2.5 are placed in the ten tubes of the front row, and the same amounts in the corresponding ten tubes of the back row. Each tube of the front row receives 0.1 c.c. of an inactivated negative serum and each tube of the back row receives 0.1 c.c. of a strong positive (amebic) serum. Normal saline is added to each tube to make up 2.3 c.c. Each tube of both rows receives 0.05 c.c. of undiluted complement. The tubes are shaken vigorously and placed in a water bath for one hour at 37° C. After the incubation five units of amboceptor in 0.1 c.c. saline and 0.05 c.c. of a 50 per cent suspension of washed sheep blood cells are added to each tube. The tubes are again shaken vigorously and placed in a water bath for one hour at 37° C. The results are then read. The largest and smallest amount of antigen giving complete inhibition with a positive amebic serum and hemolysis with a normal serum is determined. The amount of antigen midway between the largest and smallest specific dose is then selected as the antigenic dose. (See Table III).

The patient's serum: The sera are inactivated for one-half hour at 55-56° C. Fresh sera are inactivated after separation from the blood clot, and then preserved in the ice-box until used. A mixture of several normal sera are used as a negative control. In the absence of strong positive sera, immune serum of rabbits is used. The immune serum is prepared by intravenously inoculating rabbits twice weekly with saline washings of ameba cultures in increasing amounts. Six to eight inoculations usually suffice and the rabbits are bled two weeks after the last inoculation. The smallest dilutions of the immune serum still giving strong positive reactions are used in the ab-

TABLE III

Antigen titration

Tube	Antigen	Inactivated serum (½ hr. at 55° C.)	Normal Saline (.85%)	Undiluted Complement	First Incubation	5 Units Amboceptor	50% washed sheep blood cells	Second Incubation
1	0.05 c.c. 1:10	Normal 0.1 c.c.	q.s. 2.3 c.c.	0.05 c.c.	The tubes are shaken vigorously and placed in a water bath for one hour at 37° C., then are added:	0.1 c.c.	0.05 c.c.	The tubes are shaken vigorously and placed in a water bath for one hour at 37° C., and then the results are read.
2	0. 1 c.c. "	"	"	"		"	"	
3	0. 2 c.c. "	"	"	"		"	"	
4	0. 3 c.c. "	"	"	"		"	"	
5	0. 2 c.c. 1:5	"	"	"		"	"	
6	0.25 c.c. "	"	"	"		"	"	
7	0. 3 c.c. "	"	"	"		"	"	
8	0. 2 c.c. 1:2.5	"	"	"		"	"	
9	0.25 c.c. "	"	"	"		"	"	
10	0. 3 c.c. "	"	"	"		"	"	
11	0.05 c.c. 1:10	Amebic 0.1 c.c.	"	"		"	"	
12	0. 1 c.c. "	"	"	"		"	"	
13	0. 2 c.c. "	"	"	"		"	"	
14	0. 3 c.c. "	"	"	"		"	"	
15	0. 2 c.c. 1:5	"	"	"		"	"	
16	0.25 c.c. "	"	"	"		"	"	
17	0. 3 c.c. "	"	"	"		"	"	
18	0. 2 c.c. 1:2.5	"	"	"		"	"	
19	0.25 c.c. "	"	"	"		"	"	
20	0. 3 c.c. "	"	"	"		"	"	

TABLE IV

Preparations of amboceptor dilutions

Tubes	Amboceptor		Normal Saline (0.85%)	Amount Dilution of amboceptor-saline mixture	
1	0.05 c.c.	undiluted	4.95 c.c.	5.0 c.c.	1:100
2	0.2 c.c.	1:100	0.2 c.c.	0.4 c.c.	1:200
3	0.1 c.c.	"	0.3 c.c.	0.4 c.c.	1:400
4	"	"	0.5 c.c.	0.6 c.c.	1:600
5	"	"	0.7 c.c.	0.8 c.c.	1:800
6	"	"	0.9 c.c.	1.0 c.c.	1:1000
7	"	"	1.1 c.c.	1.2 c.c.	1:1200
8	"	"	1.3 c.c.	1.4 c.c.	1:1400
9	"	"	1.5 c.c.	1.6 c.c.	1:1600
10	"	"	1.7 c.c.	1.8 c.c.	1:1800

*Additional dilutions of amboceptor can be prepared, if necessary.

sence of strong positive human sera. Old, contaminated or hemolytic sera should not be used.

The complement: A mixture of sera of several guinea pigs is used instead of the serum of a single guinea pig. Otherwise the same rules apply as generally practiced in the Wassermann test. Five hundredths of a c.c. of undiluted complement is used instead of an 0.5 c.c. of a 10 per cent dilution in order to allow a greater relative volume for the serum.

Red Blood Cells: Sheep cells were selected in preference to human blood cells, the former being more available in most of the laboratories where Wassermann tests are performed. The washing and dilution of the blood cells for the test is carried out in the same way as in any other complement fixation test. Five hundredths of a c.c. of a 50 per cent suspension of red blood cells is used instead of 0.5 c.c. of a 5 per cent suspension in order to allow more volume for the serum.

Sheep blood hemolysin (amboceptor): Amboceptor is prepared in the same manner as that used in the Wassermann test. The amboceptor is titrated against fixed amounts of complement. Increasing dilutions of the amboceptor are prepared and 0.1 c.c. of each dilution is placed in a series of ten tubes. To each tube 2.3 c.c. saline and 0.05 c.c. of undiluted complement are added. The tubes are shaken and placed in a water-bath for one hour at 37° C. After the incubation 0.05 c.c. of a 50 per cent suspension of sheep cells are added to each tube. The tubes then are shaken and placed for one hour in the water bath at 37° C. The highest dilution of the amboceptor causing complete hemolysis is called one unit. Five units of the amboceptor are used for the antigen titration and the main test. The biphasic incubation in the amboceptor titration is intended to expose the complement to the incubator temperature for the same length of time as in the antigen titration and the main test. The amboceptor should be titrated each time the complement fixation test is performed. (See Tables IV and V).

The Main Test: Racks with two rows of tubes are used. The tubes of the first row receive the titrated amount of antigen, while the tubes of the second row receive saline instead of antigen and serve as serum controls. Each tube of the first and second row receives 2 c.c. of the respective serum. The last tube in the first row receives, instead of 2 c.c. serum, an equivalent amount of saline; this tube serves as antigen control. All tubes then receive saline to make up 2.3 c.c. and then 0.05 c.c. of undiluted complement is added to each tube. The tubes are then vigorously shaken and placed in the water-bath for one hour at 37° C. After the incubation five units of amboceptor in 0.1 c.c. saline and 0.05 c.c. of a 50 per cent suspension of sheep red blood cells are added to each tube. The tubes are again vigorously shaken and placed in the water bath for one hour at 37° C. The results are then recorded. (See Table VI).

Controls: (1) *Serum controls.* Each serum including the positive and negative control should have a serum control. All serum controls should give hemolysis. (2) *Antigen control.* This control should show hemolysis; inhibition of hemolysis would indicate too large an amount of antigen used in the test. (3) *Positive control.* This should always show complete inhibition of hemolysis. (4) *Negative control.* This should show hemolysis. (See Table VI).

Reading of Results: After the second incubation, the controls are examined before the unknowns. In the latter, the tubes showing the same turbidity as before the second incubation are interpreted as strongly positive (++++), tubes showing slightly less turbidity are read as positive (+++) and tubes showing only slight turbidity are called weakly positive (++ or +) respectively. Tubes perfectly transparent are interpreted as negative. The test is repeated with sera showing doubtful reactions.

TABLE V

Amboceptor titration

Tube	Amboceptor		Normal Saline (0.85%)	Complement Undiluted	First Incubation	50% sheep red blood cells	Second Incubation
1	0.1 c.c.	1:100	2.3 c.c.	0.05 c.c.	The tubes are shaken vigorously and placed in a water bath for one hour at 37° C., then are added:	0.05 c.c.	The tubes are shaken vigorously and placed in a water bath for one hour at 37° C., then the results are read.
2	0.1 c.c.	1:200	"	"		"	
3	"	1:400	"	"		"	
4	"	1:800	"	"		"	
5	"	1:1600	"	"		"	
6	"	1:3200	"	"		"	
7	"	1:6400	"	"		"	
8	"	1:12800	"	"		"	
9	"	1:25600	"	"		"	
10	"	1:51200	"	"		"	

DISCUSSION

The above described modified procedure for the diagnosis of amebiasis by means of complement fixation represents a definite improvement upon the original method. These improvements embrace a number of details. It simplifies the preparation of the antigen. It was found that repeated washings of ameba cultures do not remove a sufficient amount of bacteria to justify the effort. In addition a large number of amebae are lost as a result of these washings. On the other hand smears from washed ameba cultures still reveal a very large number of bacteria. Bacteria from ameba cultures were transferred to a series of agar plates, the growth was washed off with acetone, dried and the extract prepared in the same way as that from ameba cultures. Such extracts do not give a positive complement fixation with amebic sera. Based on these observations the washings of amebic cultures were eliminated in the modified procedure. A protracted extraction for two weeks at 55° C. results in stronger antigens than if the extraction is limited to two days as previously recommended.

Experiments with increasing amounts of serum have shown that the use of two c.c. of patient's serum instead of 0.1 c.c. or 1.0 c.c. offers definite advantages by using more antibodies and rendering the complement fixation test more stable and consequently increasing

the percentage of positive reactions. This modification of the usual complement fixation test requires detailed consideration.

In the early stage of development of the complement fixation test for syphilis several authors: Bauer (1), Stern (20), Hecht (16) and others, tried to utilize the natural amboceptor of the human serum against blood cells. These attempts failed and in general the reasons were as follows: (1) The amount of natural amboceptor varies in different serums. (2) The procedure of adjusting the amboceptor in every serum separately requires too much time. (3) It was impractical to run many tests simultaneously with such methods, and, finally (4) Frequent absence of any amboceptor or presence of it in negligible amounts in some human serums. The possible interference of the natural amboceptor on the outcome of the complement fixation test in our procedure has been avoided by using in the antigen titration and main test five units of immune serum-amboceptor thus rendering the eventual influence of natural amboceptor negligible. In addition

The beneficial improvements especially concern the early diagnosis of amebiasis, the slower gradual disappearance of positive reactions following treatment, the diagnosis in untreated and neglected chronic cases, and the differential diagnosis of other chronic disorders. An elaborate presentation of statistical findings of the improved procedure in relation to the original method and other tests is reserved for a special paper.

Amebiasis has received some attention from the public health standpoint. It was found necessary a few years ago in Illinois to develop a practical method of determining the reservoirs of infection for endameba histolytica. The examination of the feces was slow, time consuming and expensive. There were not enough trained parasitologists to do the work. It became apparent to all public health administrators that some practical method would have to be devised to determine the extent of the infection and reserve the more exact microscopic fecal examination methods for studying and substantiating some other procedure

TABLE VI

The main test

Tubes	Antigen	Normal Saline (0.85%)	Inactivated serum (½ hr. at 55° C.)	Undiluted Complement	First Incubation	5 Units Amboceptor	50% sheep red blood cells	Second Incubation
1	Titrated amount	q.s. 0.3 c.c.	Unknown 2 c.c.	"	The tubes are shaken vigorously and placed in a water bath for one hour at 37° C., then are added:	0.1 c.c.	0.05 c.c.	The tubes are shaken vigorously and placed in a water bath for one hour at 37° C., then the results are read.
2	0	"	"	"		"	"	
3	Titrated amount	"	Normal 2 c.c.	"		"	"	
4	0	"	"	"		"	"	
5	Titrated amount	"	Amebic 2 c.c.	"		"	"	
6	0	"	"	"		"	"	
7	Titrated amount	q.s. 2.3 c.c.	"	0.05 c.c.		"	"	

it has been shown that the additional amount of amboceptor caused by the presence of natural amboceptor could not affect the results, even if large amounts (2.0 c.c.) of serum are used. Therefore, a special control for natural amboceptor containing 2.0 c.c. patient's serum, saline quantity sufficient to make 2.4 c.c., 0.05 c.c. undiluted complement and 0.05 c.c. 50 per cent red blood cells suspension can be safely omitted. For the same reason it appears unnecessary to remove the natural amboceptor from the patient's serum by treating it preceding the test with washed blood cells. The changes in preparation of amboceptor dilutions and titration of amboceptor were made in order to allow more volume for the patient's sera. Smaller amounts of amboceptor are used in corresponding higher concentrations, otherwise the same amounts are tested in the same way as in the original procedure. As a result of these changes in the technique, the amount of antibodies used in this test is increased 100 per cent without changing the total volume. Proportionately the increased amount of patient's serum increases the stability of the test requiring considerably larger amounts of complement to render a positive reaction negative. The percentage of non-specific positive reactions has not been increased by these modifications.

which could be used as a practical public health laboratory procedure. We felt the need of a rapid cheap method to allow us to evaluate the relative health hazards in a community.

The relatively few cases we have been able to study lead us to believe this complement fixation method can be used for this purpose. The four plus and three plus reactions can be considered as positive. There were 87 per cent of the carriers, 90 per cent of the chronic and 80 per cent of the acute cases of amebiasis positive when we used 2 c.c. of the serum. All of these had positive stool findings.

SUMMARY

An improved procedure for diagnosis of amebiasis by means of complement fixation has been described with the following advantages:

1. Simpler preparation of a stronger antigen.
2. Increased positiveness in early and treated cases.
3. Increased stability of the test by the use of larger amounts of patient's serum.
4. A more satisfactory correspondence between this test, other ameba tests and clinical findings.

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The Digestive Qualifications of Man

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PATIENTS frequently ask physicians questions concerning the foods they should or should not eat. These questions almost invariably show that such patients have dietary prejudices. Inquiry reveals that these prejudices have arisen from one of the following causes: (1) a misinterpretation by the patient of legitimate dietary information received from physicians and dietitians; (2) an erroneous conception obtained from those whom we shall call, not for the lack of a better descriptive word, but for the sake of propriety, charlatans; and (3) erroneous information concerning the functions of the colon, the structure of the colon, and the biologic proclivities of man. Those who have dietary prejudices often believe that man suffers from digestive disorders which result from displacement of various segments of the digestive tube as a result of the evolutional influences which have caused him to assume the upright position. This information is received from various sources, frequently from the lay press. A misinterpretation of legitimate dietary information is a negligible source of confusion. A study of some of the dietary prescriptions in the possession of certain individuals reveals a most extraordinary array of ingenious combinations of foods in order to procure certain supposed physiologic effects.

A disquisition on dietary prejudices reveals that patients have spent sufficient time and energy to have become correctly informed. This situation is not the fault of physicians who are interested in diet and metabolism or the fault of well-trained dietitians. Somewhere between the dietetic experts and the general practitioner of medicine is a gap which has been generally considered nobody's field. From time to time, without any very serious thoughts on the subject, startling statements are made about what the "natural foods" for man are. Such statements bring forth arguments, often fallacious, which would indicate that man in his primitive state was either a herbivore or a carnivore.

It is the object of this communication to review what is known about the natural foods of man and to compare briefly the structure and function of the alimentary canal of man with that of the Herbivora and the Carnivora, with special reference to the so-called disadvantages which have been thrust on man's digestive equipment by his upright position.

There is not a more appropriate place to begin this consideration than by observing that the number and variety of vegetable and animal products included in the daily diet of the average healthy person are extensive. To this list of materials are added further complexities by changes which take place between the time they are collected and the time they are consumed. These changes are brought about by freezing, cooking, drying, and various degrees of decomposition; some of the changes are beneficial and some are not. In spite of partaking of this ever increasing number of foods, and notwithstanding the increasing perplexities of modern culinary art, which imparts a more luscious flavor to foods, the human race as a whole enjoys digestive health.

It is obvious that the versatility of the human digestive system, which is evidenced by the number and variety of foods ingested daily, has not been gained in recent times. This versatility, so far as the human species is concerned, is an ancient endowment. It was first manifested at a period in the past when through continental elevations and subsequent aridity of the climate the dense forests of Asia began to be thinned out and to recede toward the equator. In time these changes of the forests became great enough to bring about a shortage of food for the arboreal inhabitants, among which was man. Inasmuch as man at that time had the digestive system that we know him to possess at the present time, he was able to adapt himself to a terrestrial habitation and partake of practically any food offered by the mass of the forests and plains, and was able to eat the flesh of fish, fowl, and other animals. Through inability to obtain constant supplies of food, primitive man on occasion partook of a great variety of food in order to sustain life. To illustrate that primitive man often consumed any available food that he could lay his hands on, we may cite the fact that Mr. Cottam, of the U. S. Department of Agriculture, has recently examined for us the feces obtained from a mummy of a primitive race that inhabited the rocky shelters of the Ozark Mountains many centuries ago (1). The feces of this mummy

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contained particles of black oak acorns, fruit of the sumac, charcoal, and insects. If we could obtain comparable data on the foods of primitive peoples at the various ages of man's existence, we would have in all probability a vast amount of data to illustrate the extent of different foods that man has eaten in order to maintain health and life.

The earliest historical records of what man ate, which are comparatively recent as compared to the length of time man has existed as he now is, have been obtained from the translations of the papyri of ancient Egypt. These translations indicate that man ate animal and vegetable products and oils; the fresh leaves of the garden cress and the common mustard were eaten as salads. Grapes, figs and pomegranate were served as fruits. The ancient Egyptians did not eat much meat. They did not abstain from eating meat because they did not like it, but because they did not have it. The cow was sacred; however, it was all right to kill and eat an ox. In most districts the meat of goats, sheep and hippopotami was eaten when available. Herodotus recorded that the foods given the laborers during the building of the Pyramids consisted in large part of radishes, onions and garlic. According to translations of Homer's Odyssey, the ancient Greeks enjoyed a much greater variety of both meats and vegetables than did the ancient Egyptians. The former ate flesh of animals that we eat and enjoy, and in addition, they partook of Carnivora such as the dog and fox.

Whether the digestive system of man possesses the anatomic and physiologic qualification to digest the number and variety of foods that he eats and still enjoys digestive health, requires consideration of the chief sources and properties of the foods eaten and the digestive means of reducing these foods to end products which can be absorbed and utilized for energy by the tissues. There has been considerable experimental work done on the digestion and utilization of various foods by man, but this work alone is not enough. These experiments have been confined to the digestion of specially prepared foods consisting mainly of fats, proteins or carbohydrates. Such work seldom takes into consideration the mechanical handling of the undigestible residue of natural foods. This mechanical manipulation during digestion of natural foods is carried on by specially designed structural arrangements of the alimentary canal. The comparative anatomist is so familiar with special digestive structures which are required for the digestion of different natural foods that he can predict the types of natural foods eaten by a species.

Plants and animals are the chief sources of foods for mammals. The foods of animal origin may be divided into flesh and insects. If under natural conditions an animal partakes solely of flesh, it is designated as a carnivore; if it partakes only of plants, it is called a herbivore; and if it partakes only of insects, it is known as an insectivore. An animal that can eat either flesh or vegetable foods is known as an omnivore. This classification is helpful because it grossly predicates special anatomic structural arrangements of the alimentary tube of each group.

Before considering the differences in the structural arrangements of the digestive tubes of each group, it is well to review some of the properties of foods. All foods are chemically inactive, are insoluble under ordinary conditions, and usually are colloids. On the natural death of any food substance the chief activity is a tendency to decay. However, after ingestion of food by mammals it is subjected to the action of an organic system of catalysts known as enzymes. The

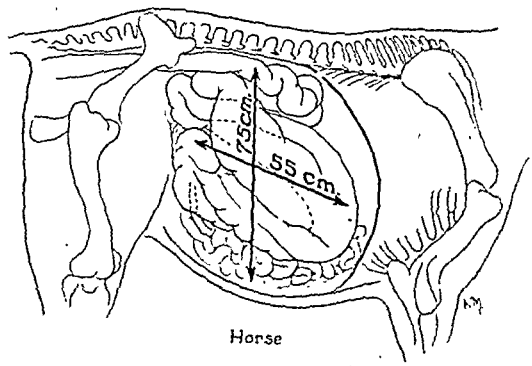


Fig. 1. Horizontal and vertical measurements of the abdominal cavity of a well developed horse.

function of enzymes is to reduce the food to simple compounds which can be absorbed. One great difference in the variety of enzymes in the secretion of various mammals is that the salivary secretion of the Carnivora, such as dogs, does not contain a starch splitting enzyme.

The great difference in the composition and digestibility of the natural foods is their varying content of cellulose and such substances as chetin, but here we are mainly interested in cellulose. Cellulose cannot be digested by the enzymes which are secreted by the digestive glands of mammals. The digestion of cellulose requires specialized structures which will retain the food long enough in the gastro-intestinal tract to make possible its digestion. Such specialized digestive apparatuses are observed in such species as the ox and the horse. Because foods which contain cellulose are less likely to undergo putrefaction than are foods which do not contain cellulose, they are susceptible to a longer retention in the body by saccular and convoluted extensions of the colon, stomach, or both. This longer retention is necessary in order that the enzyme citase, which is contained in the foods that contain cellulose, may hydrolize them to starches so that the endogenous enzymes may then proceed with the usual digestion of starch. Because of the low nutritional value of foods that contain cellulose, animals that partake of such foods under normal conditions are forced to eat constantly, and therefore there are two reasons for a great alimentary capacity.

The Carnivora may be cited as a group of mammals that do not have either a complex stomach or colon. All sections of the alimentary tube of Carnivora are supplied with thick muscles to rush the food along. That the Carnivora can maintain a healthy existence on mixed foods like those taken by man is common knowledge obtained from daily observations on the domesticated dog. In many ways the structure of the alimentary tube of the Carnivora is similar to that of man. The colon of man has rudimentary sacculations and is comparatively longer and larger in diameter than that of the Carnivora. The first half of the colon of man is somewhat similar to that of the cellulose-digesting mammals.

A survey of the structural arrangement of the alimentary tube of mammals in relation to the digestion of natural foods reveals that its length gives a great deal of information. The alimentary tube of the cat (carnivore) is three or four times, that of man (omnivore) is five to seven times, that of the ox (herbivore) is fifteen times, that of the horse is twenty times, and that of the sheep is twenty-seven times the length of the body respectively. (These measurements must not be considered absolute.) Such measurements seem to emphasize the foregoing structural considerations; they illustrate that man belongs to neither the purely Carnivora nor to the Herbivora; they bear out the fact that man possesses the simplicity of design which characterizes the alimentary tube of the Carnivora and that he possesses some of the added storage capacity of the Herbivora. These comparative differences in structure and length of alimentary tract are helpful in predicting what an animal eats under natural conditions. They indicate that if voluminous foods are to be digested, then capacity is required. They also indicate that man can partake liberally of all types of foods that do not contain large amounts of indigestible bulky matter. They further prove that man can partake of a greater variety of foods than can a carnivore, but that he falls short of the alimentary capacity of the Herbivora. Man therefore can be either a facultative carnivore or herbivore; he possesses a large part of the alimentary structural advantages of both groups.

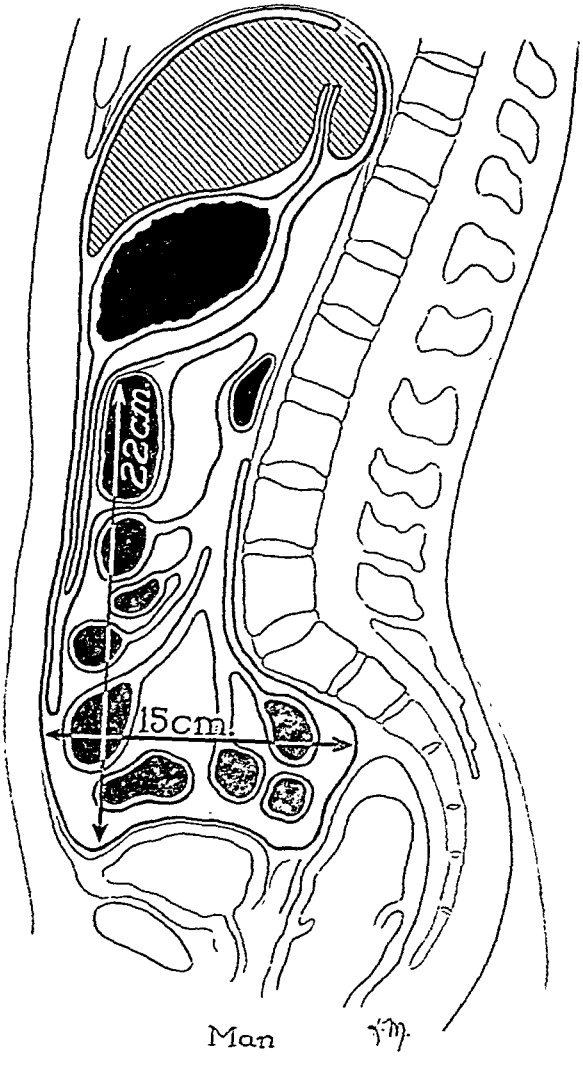
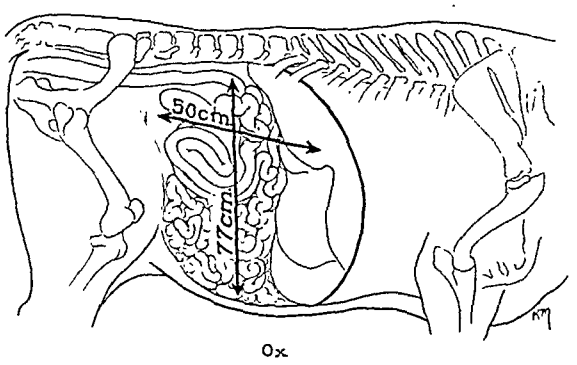


Fig. 2. Horizontal and vertical measurements of the abdominal cavity of a well developed man.

A more intimate knowledge of the structure and function of the digestive apparatus of man may be obtained by briefly reviewing the embryonic development. In a 5 mm. embryo, the digestive system is represented by a straight dorsal tube. This tube has developed embryologically from two segments, the foregut and the hindgut; each segment is found to develop further into the future anatomic structures which will carry on the three important phases of digestion. The anterior section or foregut, combined with the structures of the mouth and throat, will form the alimentary tube and digestive glands down to the distal portion of the duodenum. The distal segment of the foregut and the proximal section of the hindgut form the intestines, and the distal, or the rest of the hindgut portion of the primitive tube, when combined with the structures of the anus and rectum, forms the remainder of the alimentary canal. The function of the first portion of the digestive tube is concerned mainly with selecting, obtaining, masticating, mixing and moving the food along, and also is concerned with the beginning of chemical digestion and absorption. These very important physiologic functions, especially that of selection, cannot be overemphasized. The sight, taste and smell of food are of paramount importance and are fundamental endowments of a species. These senses initiate motor mechanisms which prepare and start the food on its way down the esophagus. These motor functions are under voluntary control. In man and the Carnivora, a protective involuntary reverse motor mechanism, vomiting, which expels disagreeable gastric contents, is operative soon after birth. Sight, taste, smell and the forcing of the food into the esophagus by the voluntary act of swallowing, produce the involuntary motor mechanism of peristaltic action and the secretion of digestive juices. Once the food is in the stomach, the additional factor of gravity is operative. These involuntary forces end with the voluntary discharge of the alimentary dejecta, which is controlled by the anal sphincter. All the accessory digestive glands that pour their secretions through ducts into the digestive tube are developed at appropriate levels. These glands and their secretions usually are similar in structure and function in all mammals. Their differences depend on the concentrations of their secretions and quantity of secretion required at a given time. The function of the enzymes is the same; they are catalytic agents which fit into the complex molecules of the food like a key into a lock. This linkage permits chemical reactions to take place with the formation of compounds which can be absorbed. It is only necessary to state that there is no part of digestion which has received more attention than the function of enzymes. However, digestive disorders that are the result of a deficient supply of enzymes or an overproduction of these organic catalysts are indeed few in number.

Primitive man learned that he might tamper with his daily intake of food and include fasts in his religious ceremonies. However, the regular intake of water was never interfered with; no matter how religious he might feel, man usually allowed himself



Ox

Fig. 3. Horizontal and vertical measurements of the abdominal cavity of a well developed ox.

water to drink. His places of abode were always near a constant supply of water; if he lived in a cave, a stream was nearby. Since the emergence of our piscine ancestry from the sea, the greatest battles for survival have occurred in the vicinity of watering places. Some orders of mammals, the Ruminántia, have special structural arrangements in their stomachs for the storage of water. A more helpful appreciation of the services rendered by water in the processes of digestion and assimilation may be gained by contemplating the actual rate of turnover of this remarkable solvent and carrier by the various digestive organs of man. The salivary glands, stomach, intestinal walls, pancreas, and the lymph return to the blood the water that they drain from it. The minimal volume of water returned in this way is 4000 c.c. A more liberal estimate for this returned volume of water would be 10,000 c.c. At every point in the gastro-intestinal tube attempts are made to conserve and to return to the body certain quantities of water. Some water is lost in the feces, but under normal conditions it is the function of the colon to keep this loss of fluid at a minimum. Under most circumstances the sensation of thirst is adequate to maintain a sufficient quantity of water for digestive processes. However, recently acquired sedentary habits have dulled our sensations, and sufficient amounts of water may not be taken. Of the various types of starvation, the complete deprivation of water leads most rapidly to a fatal termination. A lack of sufficient water may lead to digestive disorders which will be relieved by an adequate intake of water.

When water is ingested, it leaves the stomach rapidly. With the sweeping out of the acid secretions of the stomach, the intestinal fluids become more acid. The osmotic pressure of the intestinal fluids is decreased until an equilibrium is reached. The aqueous portion of the chyme throughout the midgut thus remains in constant electrolytic equilibrium with the extracellular fluids of the body. It is this constancy of electrolytic equilibrium and temperature that makes possible the constant efficiency of the action of the enzymes.

As has been stated, the colon of man in its proximal half is thin-walled, somewhat larger in diameter, and longer than that of a carnivore of comparable size, and in addition the human colon has rudimentary sacculations. These sacculations might create superficial speculation that the colon of man possesses digestive functions, and that man is therefore closely related to the Herbivora. Welch (2) recently has determined that the digestion of organic materials, such as proteins, carbohydrates and fats, is completed in the small intestine of man.

Because of the upright position of man, the alimentary substances are moved against the force of gravity in passing from the pelvic coils of the small intestine to the hepatic flexure and again in passing the proximal part of the left half of the colon to the splenic flexure. These obvious facts have caused considerable speculation by pessimists who believe man is biologically inferior. We have made investigations to determine if a comparable situation existed in some of the domesticated four-footed animals. In order to make these comparisons, dissections and measurements were performed on the horse, the cow, the pig and the cat. During these dissections the idea occurred to us that the possible distances that the alimentary substances might be raised against gravity in any species was limited by the following conditions: (1) the vertical diameter of the abdominal cavity and the variations of the distances which are brought about by changes in position; (2) the length of the mesentery which controls the distance that any segment of gut may move within the abdominal cavity during changes in position; (3) the degree of the fixation of the intestines, especially the colon, at flexures; and (4) the tonicity and elasticity of the abdominal wall.

The vertical diameter of the abdominal cavity represents the maximal distance that the alimentary substances may be moved against gravity. However, no species keeps the abdomen in the same position all the time. In this study it was impossible to compare more than the upright or standing position. By dissection and measurements it was found that when the animals studied were in the upright position the length of the mesentery permits the small intestine to reach and normally occupy the most dependent portion of the abdominal cavity, and that some part of the colon is always attached to the uppermost part of the abdominal cavity. The length of a line which connects the dependent portion of the abdominal cavity with the upper part is therefore the distance the alimentary substance must be raised against gravity in every case. Thus, our problem in comparing the distances the alimentary substance is raised against gravity in all the species was simple and could be determined with a fair degree of accuracy. The measurements shown in Figures 1, 2 and 3 illustrate the distance the alimentary substance is raised against gravity. For man, this distance is proportionally no greater than for the animals studied. The greater fixation of the colon of man is probably advantageous. If there should be only slight fixation of the human colon there still would not be proportionally any more work done by the intestines of man than is done by the intestines of the horse and cow.

SUMMARY

It is a fundamental endowment of the human species to eat a larger number and variety of foods than does

any other mammal. Any food is "normal" for man so long as it does not contain large amounts of cellulose, chetin or similar materials which require specialized anatomic structures for storage and digestion. Specialized anatomic structures limit the kinds of foods which may be eaten by the animal that possesses them. Man is a facultative carnivore and herbivore. He possesses the common enzymes of both species with increased storage capacity over the Carnivora and decreased complexity of stomach and colon over the Herbivora. The upright position assumed by the human species does not in any way hinder, hamper or decrease the digestive efficiency. The digestive system of man as we know it is a fundamental endowment; it is one of the greatest attributes he possesses, and is to a large extent responsible for obtaining his so-called preeminence over all living things. Criticisms of this remarkable system because man assumes the upright position are destructive, founded on false assumptions, and serve no purpose other than to create apprehensions in the minds of those who are unable through lack of training or opportunity to make first hand comparisons of the various digestive systems of mammals.

In considering diets and giving dietary instructions to patients, if the occasion arises, it should be emphasized that man is superior to all other mammals in the number and variety of foods that he may eat and digest, and that the number and variety of foods that he may eat is limited only by his alimentary capacity. However, the possession of these superior digestive qualifications does not warrant abuse. The cellulose of food is largely indigestible. Moderately large amounts of this material may be eaten without producing digestive disorder. The same is true of dirt and other foreign materials, but such practices are not to be sanctioned. Emphasis should always be placed on the fact that the upright position has given man no digestive handicaps. Supposed symptoms attributable to "stasis" and "angulation" of any part of the alimentary canal as a result of the upright position are spurious. In short, man is anatomically and physiologically superior in his digestive functions, the same as he is supposed to be in his intellectual attainments over all living things.

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Causes of Mortality Among Diabetics

By

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WHEN we look upon the mortality tables in such exhaustive studies as those of the Metropolitan Life Insurance Company, Chart 1, we can see clearly that diabetes is practically at the bottom of the column, only 28 cases dying each year in 100,000 population as against 261 dying from the diseases of the heart. But even such a number represents some 35,000 cases of people having diabetes dying each year in this country.

If we consider our population as 125 million and the total number of diabetics in this country as one million, then if no new cases came up, the total diabetic population would die out in 28 years. However, if we consider for the sake of argument, that our diabetic population is at a fairly steady level, d.e. that as many new cases develop as the number that die, then we must reason that there are some 35,000 new cases of diabetes developing each year, an incidence of .028 per cent, which would mean that in a city of one million population there should be some 280 new cases of diabetes each year and also some 280 deaths from the diabetic ranks yearly.

When a diabetic patient dies, the death certificate usually bears as the cause of death the simple statement of "diabetes." This naturally introduces a grave error into our statistical studies as it shows that the mortality rate from diabetes is on the increase, as the extensive studies of the Metropolitan Life Insurance Company seem to indicate. However, is this truly so? Do these patients die *of* diabetes or merely *with* diabetes? I have attempted in this study to analyze the mortality data from my own series of 4744 cases of diabetes of whom 527 died over a period of 15 years, and it is the study of this group of 527 cases which I am here presenting.

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I have put to myself three questions which I shall attempt to answer: 1. At what age do most diabetics die? 2. What is the cause of death in these diabetics? 3. How long have they had their diabetes at the time of death?

THE AGE AT DEATH

Chart 2 presents the distribution of these 527 cases that died, arranged according to the decade of life in which they died. Sixty-nine per cent died in and above the sixth decade and 31 per cent in from the first to the sixth decade. Almost 50 per cent died in the seventh and up decade.

On that same chart I drew a curve of the mortality rate in non-diabetics this strictly speaking includes diabetics, these representing about one per cent, thus an insignificant factor from a large series of 41,233 deaths reported from New York City in 1933 by Bolduan. Curve "a" represents this series and the interesting point is that the curve is practically parallel to my curve of diabetics. This fact alone shows that as far as mortality in diabetics and non-diabetics is concerned, about the same percentage of each die in their respective decades, in other words, diabetes presents no striking difference in the mortality-age-incidence.

In curve "c" I plotted the experience of Bolduan and Weiner in 1272 cases of diabetic deaths and there too,

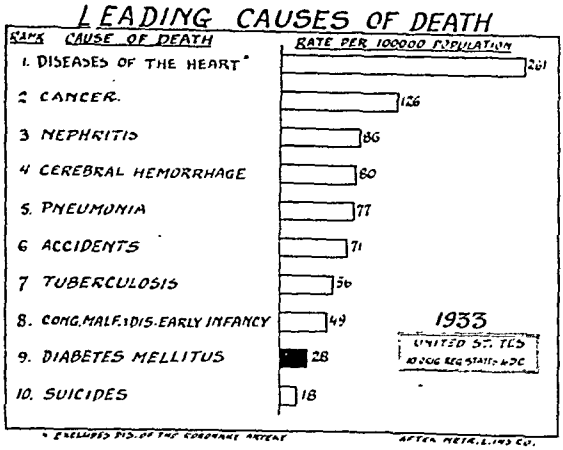


Fig. 1. Leading causes of death in ten original registration states and District of Columbia after Metropolitan Life Insurance Company.

can be seen a curve fairly parallel to mine which, I feel, substantiates these data.

In New York City where nearly one-third of the population is Jewish, Bolduan and Weiner gathered some interesting statistics. In 1931 there were 41,233 total deaths, and of these 14,047 or 34 per cent were Jews, and 27,186 or 66 per cent were non Jewish white. In this same group of deaths the diabetic deaths comprised:

	Jewish	Non-Jewish
	602	670
Per cent of total mortality	4.29	2.45
Per cent of group mortality	4.3	2.4

These figures show that mortality among the diabetics is twice as much among the Jews as it is among Non-Jewish whites with diabetes. This I think is quite a significant figure.

The fact that upward of 50 per cent of people with diabetes die beyond the seventh decade throws the weight of mortality toward the old age, when a mortality is more or less expected even in non-diabetics. Thus one would reason that diabetes here plays a comparatively small role, for the mortality in the early decades is comparatively insignificant. Having crossed half a century of our life line, we have to be prepared for accidents which may and do happen, for the best part of life, as far as duration is concerned, is over.

Thus we can summarize, that those having diabetes as a rule do not die young, but rather toward the other end of the natural life line, in the same relative ratio as the non-diabetic, and we can step up to consider point two.

THE CAUSE OF DEATH IN DIABETES

What is the actual cause of death in diabetics? Chart 3 and Table I present these data. Here the outstanding factor is cardio-renal disease, which again is largely a disease of old age, a degenerative disease. Even if we withdraw the purely renal disease, the uremia, which I placed at the top of the cardia-renal column, the length of the column is still entirely out of proportion to all other causes of death. Blotner, for instance, reports a mortality rate of 45 per cent in coronary occlusion in all cases of diabetes coming to necropsy at Peter Bent Brigham Hospital. In non-diabetics over forty years of age the disease was found in 21 per cent. He says that in 43 per cent of all the series the chief cause of death was directly attributed to cardiac disease. But there are so many things that diabetics can die of, the same as non-diabetics, for diabetes does not carry with it an immunity to other accidents. Hajek points out that fact that arteriosclerosis which in his series of cases in 1920-1921 represented 28 per cent rose to 60 per cent in 1931-1934 as cause of death, where as coma which in the first series was 54 per cent fell off to zero in the last series. If we consider the deaths in my group of 527 cases which are purely due to diabetes, namely coma, we see that the actual percentage as compared with all other causes is comparatively insignificant, comprising but 11.1 per cent of the total mortality. Thus we could say that only 11.1 per cent of all deaths in this group was actually due directly to diabetes. We can go a step further and say that even this per centage could be lower by proper and adequate care, for my figures among children in coma mortality rate were 3.2 per cent, and in adults 5.6 per cent. Thus an average of 4.4 per cent or practically one-third of those in this series which includes cases from my series of diabetics taken care of during coma elsewhere, and

TABLE I

Causes of mortality in diabetes

Author	No. Cases	Card. Renal	Mortality Per Cent					
			Inf. Dis.	Coma	Ca.	TB	Pneumonia	Misc.
Hajek	22	27	18	54				
Hajek	101	50	35	5	9			
Sevringhouse	79	44*		14	3	5	20	12
Holcomb	168	25	2	60	3		3	5
Hekimian	84	45	20	24	3	7		
Joslin	104	43			28		2	9
John	327	40	6	11	10	5	9	19
Total Average %	1085	39	16	28	9	6	8	

TABLE II

Diabetic mortality according to length of diabetes in 527 cases that diet. Male 264, female 263.

Decade		I M	I F	II M	II F	III M	III F	IV M	IV F	V M	V F	VI M	VI F	VII M	VII F	Total	%
3	MONTHS	3	7	2	3	2		2	5	5	4	7	7	13	5	65	12.2
6			3	2		2	2	2		4	4	5	6	7	10	47	9.
1	DIABETES — YEARS — DURATION	3	2	3	2	1	2	1	5	9	11	8	10	19	17	93	17.6
2		2		1					1	6		3	9	7	6	35	6.6
3		1	2			1	1	1	2		1	4	5	12	16	46	8.7
4				2		1	2	1	1	2	4	2	2	10	6	33	6.2
5		2				1		1	1	3		5	1	9	7	30	5.7
6					1	1	2				3	7	7	6	9	36	6.8
7				1		1			1	1		5	1	6	3	19	3.6
8					2		1	1		2	2	3	1	6	6	24	4.5
9							1	1				1	3	3	1	10	1.9
10								1		1		3		3	8	16	3
11												2	1	2	2	7	1.4
12					1			1			1		1	3	1	8	1.5
13											2	1	1	3	4	11	2.1
14											1		2	2	1	6	1.2
15												2	2	5	7	16	3
18										1		1	1	6	4	14	2.6
21							1					2		1	3	7	1.4
24						1								1		1	.19
27															1	1	.19
30														2		2	.38
Total		11	14	11	9	11	12	12	16	31	33	61	60	126	117	527	
Per cent		4.8		3.8		4.4		5.3		12.7		23		46			
Average duration of life after diabetes. Years.		1.24		2.9		4.73		3		3.23		4.91		6			
Heikimian & Vogel for comparison.		1/12		3		4.5		4.2		4		7		7			
Died in the first year of diabetes—%.		72.		60.		39.		54.		55.		35.		29.			

furthermore it dates back into the preinsulin era.

It is evident therefore that patients who have diabetes rarely die of diabetes. They die of something else. We need badly a revision of our mortality statistics in this country, and I dare predict that as our younger generation of physicians go out, with much better training than we older men had, we will see the true mortality rate in diabetes falling. Thus when we watch the rising curve of diabetic mortality gathered by the Metropolitan Life Insurance Company statistics, we have to take it with a bit of reservation. In my estimation the mortality rate due purely to diabetes is not high.

Of course, we can go a step further and reason how much, for instance, does diabetes contribute to the cardio-renal question, the arterio-sclerotic gangrenes, but that is another problem which will require close statistical, X-ray and biochemical studies which will have to cover a period of many years. It is a good project for some younger man to undertake as a life study, a problem which will be very important scientifically and statistically.

DURATION OF DIABETES

How long have these patients who died had diabetes? We can gather this interpretation from Table II, in which I have analyzed this group of 527 deaths among diabetics according to the length of diabetes and their death in the various decades. One needs but consider the data in the column of "average duration of life after they developed diabetes." In this group, the older the person is when he develops diabetes, the longer his life line. We start with 1.24 years in the first decade and wind up with 6 years in the seventh and above decade; thus the span is five times longer when the diabetes develops in advanced years. We speak of the fact that the first year of life following the discovery of diabetes is the most important period. They either make the grade or they do not. After the first year the road is much easier to trod, for by that time the patient has acquired a certain dexterity in the handling of his problem and his chances are better. This accounts largely for the shorter span of life in the earlier years, an inability of one's adapting himself to this new problem.

It is not merely the diabetes itself which is the de-

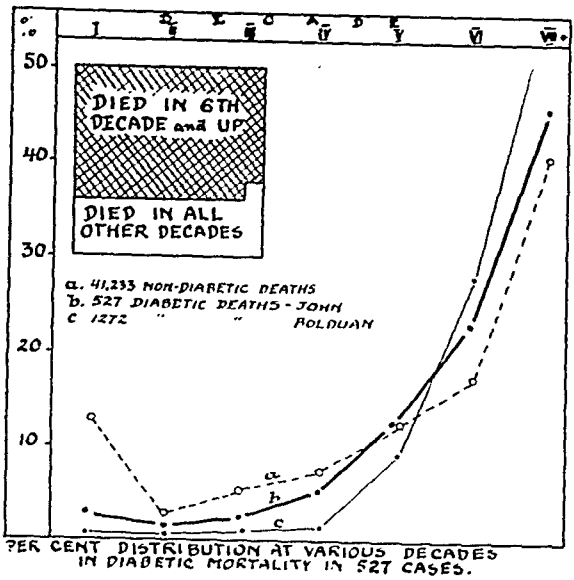


Fig. 2. The per cent distribution at various decades in diabetic mortality in 527 cases.

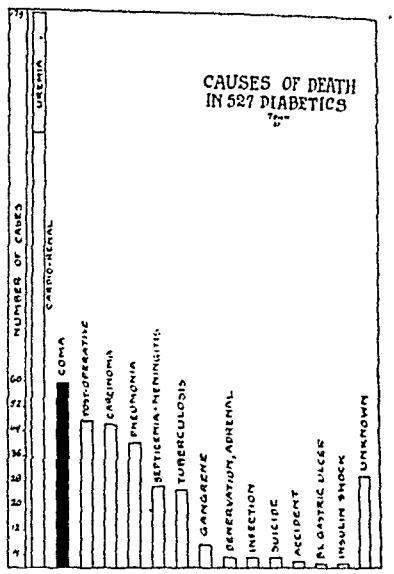


Fig. 3. Causes of death in 527 diabetics.

ciding factor. There are many other factors which enter the question of longevity. Let us take for instance the simple question of obesity which too is quite dominant among the diabetics. Again we shall turn to the large statistics of the Metropolitan Life Insurance Company, a publication by Dublin who shows that the question of mortality per 100,000 arranged according to weight is as follows:

Mortality of those of normal weight	14 per M.
Mortality of those 15-14 % below nor. wt.	9 per M.
Mortality of those 15-34 % below nor. wt.	9 per M.
Mortality of those 5-14 % above nor. wt.	22 per M.
Mortality of those 15-24 % above nor. wt.	45 per M.
Mortality of those 25-up % above nor. wt.	117 per M.

You can readily see how this factor alone would change the pure mortality picture in diabetics if one author reported a series of cases of normal weights or below and another author a series of much over-weight patients. And there are other factors of a similar nature which enter into the picture and which complicate it so that at best, our statistics are somewhat fragmentary.

SUMMARY

This study of rather a small group of cases of diabetics shows clearly enough, I think, that diabetics do not die early in life as a rule, but largely late in life when life is already on the descent; that they do not die because they have diabetes, but largely because of some other condition which can befall any non-diabetic; that the older they are at the time that diabetes develops, the better chance they have for a longer span of life. I wish to emphasize the need for improved mortality statistics.

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A Study of Gastric Emptying with the Pylorus Open*

By

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and

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THIS research was undertaken to determine if possible whether the delay in gastric emptying known to follow the addition of such substances as HCl, dextrose, fat, etc., to a test meal is the result of "closure of the pylorus" as frequently stated or is due to some other cause. It is a part of a more general study of the mechanism that regulates the emptying of the stomach, in which we have been engaged for a number of years (1, 2, 3).

The usual method of investigating the problem has been to remove the pylorus surgically, and then to determine whether the emptying of various materials from the stomach was hastened, or still proceeded in an orderly manner. This type of experiment was apparently first performed by von Mering (4), who studied dogs after resecting the pylorus and observed that the emptying of water, milk and sugar-peptone solutions from the stomach occurred at intervals as usual and was neither slower nor faster than normal. More recent investigations have given similar results.

Thompson (5) removed the pyloric sphincter along with more or less of the pyloric portion of the stomach in a large series of dogs. In most of the animals the continuity of the tract was re-established by means of a Polya gastrojejunostomy. He was primarily interested in the secretory changes following operation and discussed the effects on emptying time but briefly. We have therefore obtained his permission to report the following private communication (6): "In my observations on the emptying rate of the stomach in dogs after resection of the pyloric sphincter, the results varied with the test meal and the method of observation. Using the opaque meal in roentgenologic studies, the time required for the emptying of the stomach was shortened after operation in 80 per cent of the animals. Using the meat-water meal in fractional analyses, the emptying time after operating was prolonged in 67 per cent of the animals. I attribute this difference to the nature of the test meals used keeping in mind the fact that the meat-water meal is normal and that the barium-acacia-milk meal is not normal for the dog. I conclude therefore that more time is required for the stomach to empty itself of the food in the normal diet following resection of the pyloric sphincter than is required when the sphincter is intact."

These results were probably influenced to some extent by the fact that in most of the operated animals the stomach emptied into the jejunum, instead of the duodenum which is the source of many important regulatory influences affecting gastric motility.

Gianturco (7, 8) studied the effects of gastro-enterostomy and of pyloric excision in cats on the rate of gastric emptying of fat, hypertonic solutions of sugar and salt and of water. He observed "hardly any difference" between the emptying times after the operations and those of normal cats. "We were forced to conclude," he says, "that the pylorus is not responsible for delayed emptying of oils and concentrated solutions of salt and sugar."

Chrysler and Van Liere (9) found that sectioning the pyloric sphincter, gastro-enterostomy, or partial parasympathetic denervation of the pyloric sphincter in dogs did not decrease the gastric emptying time. Ravdin (10) observed that the amount of glucose solution remaining in the stomach after one hour was not reduced following gastro-enterostomy, Polya or Billroth I operations. Ravdin, Pendergrass, Johnston and Hodes (11) performed similar experiments using oils, protein and hypertonic glucose solutions as well as water barium mixtures, and found that operations designed to eliminate the restraining function of the pylorus did not hasten the emptying.

Pyloric resections, gastro-enterostomies and similar operations on patients should provide an abundance of material for studies of pyloric function in man, but little exact information is recorded. More or less signficant studies have been reported by Gaither (12), Kirschner (13), and Beresow and Stern (14), all indicating that, except in occasional instances, the operations referred to do not hasten the emptying of the human stomach. Beresow and Stern studied 25 cases after Billroth I operations and found very rapid (blitzartige) emptying in three. In five others the emptying was somewhat accelerated but orderly; in the remainder it was normal. Somewhat different results were reported by Shay and Gershon-Cohen (15), who found that in the cases reported fats and solutions of different osmotic pressures did not delay gastric emptying to the same degree in stomachs with resected pylorus as in the intact stomach. Since they were dealing with achlorhydric patients, their results do not provide a basis for generalization.

Best and Taylor (16) state that, "X-ray examinations of the stomachs of patients in whom the pylorus has been excised, show emptying times which do not differ appreciably from the normal (Singleton)." Dr. Singleton (17) advises us that the statement refers to unpublished observations made in "the examination of a number of cases who had Billroth I operation for duodenal ulcer, cases in which the pyloric sphincter and the duodenal caput only were excised and end-to-end gastro-duodenostomy performed. These cases obviously have no sphincter left, in spite of which the emptying time of their stomachs was within normal limits." Dr. Singleton further points out the

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TABLE I

Summary of results of 194 observations of gastric emptying in two animals

GASTRIC CONTENTS (300 c.c.)		AMOUNT REMAINING IN THE STOMACH						EMPTYING TIME		
		After 10 minutes			After 25 minutes					
		Controls		Pylorus open	Controls		Pylorus open	Controls		Pylorus open
		Normal c.c.	Dummy c.c.	c.c.	Normal c.c.	Dummy c.c.	c.c.	Normal min.	Dummy min.	min.
0.9 PER CENT NaCl										
Dog No. 1 male	Max.	120	150	155				30	30	30
	Min.	41	10	0				10	10	6*
	Average	(11) 72	(10) 67	(10) 93				(11) 19	(10) 18	(10) 22
Dog No. 2 female	Max.	130	150	175				25	35	35
	Min.	55	85	55				15	15	15
	Average	(12) 105	(6) 115	(7) 126				(12) 17	(6) 23	(7) 26
N/20 HCl										
Dog No. 1 male	Max.	260	230	265	180	140	210	50	50	60
	Min.	175	200	110	60	115	75	35	40	45
	Average	(5) 203	(7) 208	(8) 221	(5) 116	(7) 129	(8) 163	(5) 42	(7) 45	(8) 47
Dog No. 2 female	Max.	245	220	225	145	150	175	55	55	65
	Min.	175	215	210	80	105	120	35	40	45
	Average	(7) 206	(4) 216	(6) 212	(7) 116	(4) 131	(6) 151	(7) 42	(4) 47	(6) 52
5 PER CENT GLUCOSE										
Dog No. 1 male	Max.	205	155	200	151	130	140	60	60	50
	Min.	80	75	100	35	0	70	25	20	35
	Average	(6) 117	(6) 112	(6) 147	(6) 83	(6) 80	(6) 97	(6) 38	(6) 42	(6) 40
Dog No. 2 female	Max.	190	180	215	170	130	150	75	55	65
	Min.	130	155	155	85	70	65	35	40	35
	Average	(6) 168	(6) 164	(6) 187	(6) 123	(6) 93	(6) 117	(6) 53	(6) 43	(6) 51
10 PER CENT ALCOHOL										
Dog No. 1 male	Max.	225	215	170	150	200	195	120	115	100
	Min.	85	135	105	95	115	85	75	90	105
	Average	(6) 146	(6) 167	(6) 140	(6) 125	(6) 148	(6) 139	(6) 100	(6) 102	(6) 132
Dog No. 2 female	Max.	225	310	165	250	325	175	165	80	115
	Min.	115	160	145	100	90	90	55	45	75
	Average	(6) 167	(6) 212	(5) 158	(6) 157	(6) 162	(5) 146	(6) 93	(6) 63	(5) 96
OLIVE OIL		After 30 minutes			After 3 hours			hrs.	hrs.	hrs.
Dog No. 1 male	Max.	180	210	245	143	160	140	5.16	5.5	5.0
	Min.	115	140	140	70	42	100	3.5	3.0	5.0
	Average	(3) 145	(5) 185	(4) 194	(3) 117	(5) 90	(4) 122	(3) 4.55	(4) 4.0	(3) 5.0
Dog No. 2 female	Max.	240	210	255	175	35	195	4.5	3.0	7.0
	Min.	25	145	70	0	22	75	0.5	3.0	4.5
	Average	(10) 138	(2) 177	(6) 187	(10) 79	(2) 28	(6) 147	(10) 3.15	(2) 3.0	(5) 5.5

impossibility of obtaining normal controls in such cases, because of the pathologic state existing prior to the operation.

In the absence of opposing data, it is reasonable to conclude that pyloric resection or other operations with a similar functional significance do not shorten the *total emptying time* of the normal stomach of man or of certain experimental animals. However, when the *rate* of emptying during the first few minutes after feeding is observed, the results are somewhat different. Cannon and Blake (18) found that after pyloroplasty (in cats) the exit of carbohydrate and protein food from the stomach began earlier and progressed somewhat more rapidly than in normal animals. McCann (19) observed that in a dog after resection of the sphincter more of a meal consisting of meat and water had passed into the intestine in twenty-five minutes than was noted at the same period of digestion in a normal animal. Pannett (20) found that after pyloroplasty (in cats) food passed into the duodenum and jejunum more quickly during the early stages of digestion than in normal cats. He could not affirm, however, that the accelerated passage was maintained during the later stages of digestion.

The investigations reported, although they are significant, fall short of furnishing a final solution of our problem. Gastro-intestinal operations may, for various reasons, be followed by delayed gastric emptying which would conceal the effect of loss of pyloric function. Removal of the pyloric sphincter may not abolish the sphincteric function, which may, conceivably, be assumed by adjacent rings of antral muscle. Meyer and Schmidt (21) consider the possibility of a sphincter-like action of the muscle surrounding any gastro-intestinal anastomosis. There is the further difficulty in operative experiments that the control observations and the experimental studies must be separated by a considerable time interval during which the characteristic emptying time may change.

METHOD

The method of study that we have used provides for eliminating the sphincteric function of the pylorus without interrupting the continuity of the gastro-intestinal tract. It provides also a means of determining whether the sphincteric function is, in fact, absent and of making con-

trol and experimental observations on alternate occasions.

Dogs were used, provided with gastric and duodenal fistulas in a manner described in detail elsewhere (2). The fistulas were fitted with stoppered cannulas of hard rubber; after healing was complete, the tendency to leakage was well controlled. Such animals live indefinitely, barring accidents to the cannulas, and show no nutritive disturbances traceable to the fistula operations. The gastric fistula was placed near the greater curvature in the body of the stomach, well away from the pyloric antrum. The duodenal fistula was between six and eight inches from the pylorus. Both fistulas were so placed in the abdominal wall as to bring about a minimal displacement of the viscera.

To measure the emptying time, the test material was allowed to flow into the empty stomach through a tube passed through the stopper in the gastric cannula. The entire contents were then withdrawn at appropriate intervals through the same tube into a graduated cylinder, the quantity noted, and the material returned to the stomach. The "emptying time" was recorded as the time required for the stomach to reduce its content to 50 c.c. or less. All the materials were liquid and were at room temperature when placed in the stomach.

Because of the occasional presence in the "empty" stomach of various amounts of gastric juice, food residues, hair, etc., which tended to cause variations in emptying rates, we adopted the practice of washing out the stomach and duodenum with water and filling the stomach with 300 c.c. of saline, which was permitted to remain until emptied normally before beginning observations. The emptying time of this "washing out" saline was not recorded; it was observed and, if it was unusual, observations were postponed until the saline emptying time returned to within normal limits.

To eliminate the sphincteric function of the pylorus, an open aluminum tube was placed in the pyloric orifice and held in place by means of pieces of rubber tubing attached to its two ends and brought out through the stoppers in the cannulas (Fig. 1). The gastric contents were free to enter the lumen of the aluminum tube through four ¼" holes near its gastric end and to pass into the duodenum through holes in the wall of the rubber tube attached to the duodenal end. The outer ends of the rubber tubes were closed with clamps. It was possible to demonstrate the patency of the pylorus by opening the outer end of the duodenal tube and draining out the entire contents of the stomach through the tube in the pylorus. The material flowed in a steady stream the full diameter of the tube and was all out in less than one minute. By this procedure occasional accidents, such as plugging of the tube with mucus, displacement of the apparatus, etc., were readily detected, and we are confident that the pylorus was actually open throughout the experiments that are so recorded.

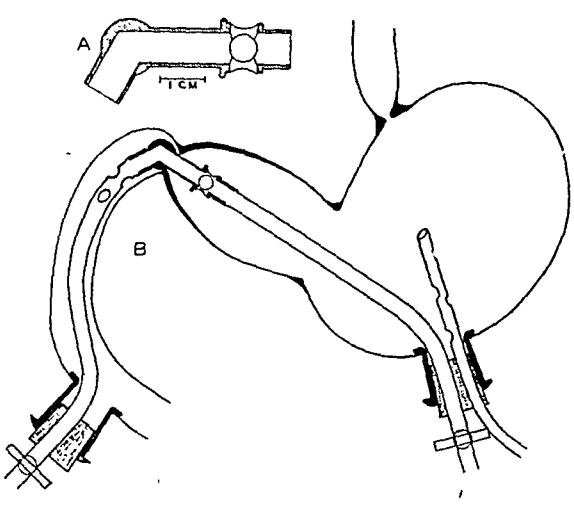


Fig. 1. Diagram of apparatus used to keep the pylorus open. Insert (A) is a scale drawing of a section through the pyloric tube. The gastric contents passed through the lumen of this tube and therefore encountered no resistance due to the pylorus. An apparatus of identical shape and dimensions but without holes in the gastric end was used in approximately half of the control experiments (dummy controls); in these the gastric contents necessarily passed between the outer surface of the tube and the pyloric sphincter.

Three types of experiments were performed with each of the materials investigated: (1) normal controls to determine the emptying time in the absence of any apparatus, (2) dummy controls with an apparatus in the pylorus identical externally to the open pyloric tube but without holes, and (3) experiments with the open tube in place (pylorus open).

SOURCES OF ERROR

The animals were abnormal in that they had gastric and duodenal fistulas. There is no evidence that the emptying times were influenced by this fact, but we do not present the normal controls as measurements of the normal emptying time for the materials studied. The frequent emptying and refilling of the stomach also may have influenced the emptying time. These and other important conditions were the same in all the experiments and could not have determined the difference or lack of difference in emptying times observed in the experiments with the pylorus open as compared to the controls.

The most serious objection to the method is the necessity for placing apparatus, tubes, etc., in the stomach and duodenum. This difficulty was partially overcome by control experiments with the dummy apparatus in position so that whatever irritation the apparatus might cause would have an equal opportunity to affect the control results. However, it is evident that the dummy apparatus tended to obstruct the pylorus and thus introduce a condition not present in any of the other experiments. This difficulty was evident during approximately the first thirty minutes after placing the apparatus; after that time it did not appear to influence the results. Whatever influence it may have had would have been opposite to the general trend of the results and may therefore be disregarded.

RESULTS

The emptying times of the stomach for 300 c.c. 0.9 per cent sodium chloride solution, N/20 hydrochloric acid, olive oil (100 c.c. plus 200 c.c. of normal saline), 5 per cent glucose solution and 10 per cent ethyl alcohol in normal saline were studied. The N/20 HCl was prepared in approximately isotonic solution by mixing equal parts of N/10 acid and normal saline. Normal controls, dummy controls and experiments with the pylorus open were recorded for each substance. The average emptying times as well as the amounts remaining in the stomach after 10 and 25 minutes (for olive oil after 30 minutes and three hours) are shown in Table I. The number of experiments of each type is shown in parenthesis beside the averages.

The average emptying times, except for olive oil, were not significantly influenced by the different experimental conditions. Keeping the pylorus open did not accelerate the emptying of any of the substances investigated. The partial obstruction of the pylorus with the dummy apparatus also failed to alter the emptying time. There was a consistent, and probably

significant, delay in the emptying of oil when the pylorus was open as compared to the controls.

In Fig. 2 the average amounts of the various substances remaining in the stomach at regular intervals after filling are shown graphically. These curves give an idea of the rate of emptying during the various phases of the emptying process. Each of the curves except the dummy control curves for alcohol was plotted from the averages of all the results obtained under the stated conditions with both animals. In one animal the emptying of alcohol with the dummy apparatus in place was unaccountably rapid; for this reason the dummy control experiments with alcohol were plotted separately for the two animals. With this exception and again with the exception of olive oil the average

the emptying of acid is regulated by means of a reflex mechanism having a short latent period and therefore fully operative from the beginning, whereas the emptying of glucose is controlled by a humoral mechanism with a relatively long latent period which would permit rapid initial emptying. Whatever the regulating mechanism may be, it is evident that its essential characteristics as they affect the curves were not materially modified by keeping the pylorus open.

To determine whether the stimuli that controlled the emptying in these experiments acted within the stomach or only in the intestine, additional experiments were performed in which the duodenum was drained. The dummy apparatus was used because it provided a convenient means of anchoring a drainage

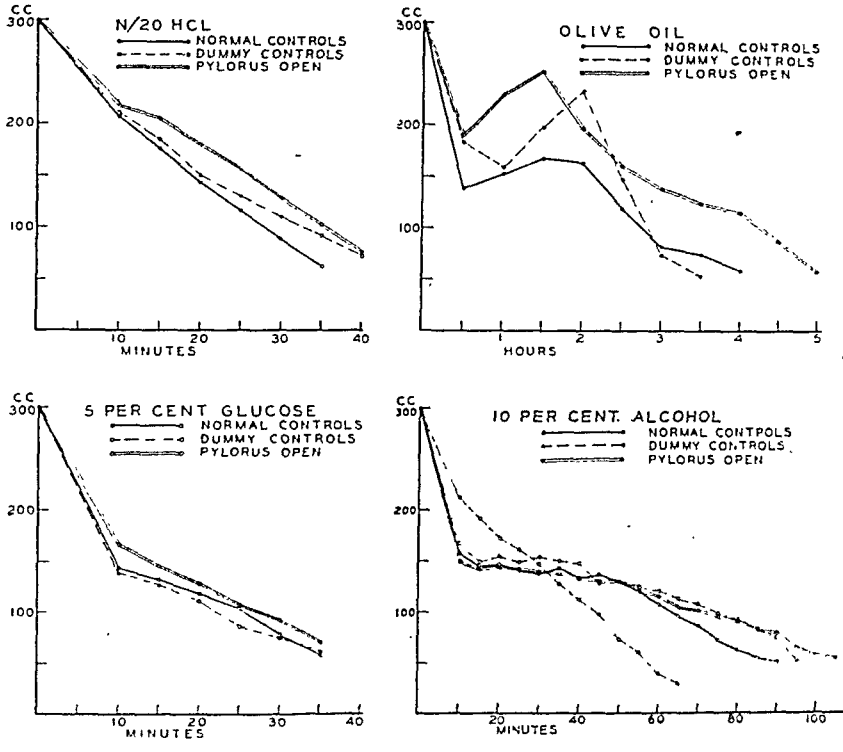


Fig. 2. Curves showing the rate of exit of various materials from the stomach under different experimental conditions. Ordinates represent the amounts remaining in the stomach, abscissas the elapsed time after filling. With certain exceptions mentioned in the text, the data were obtained by averaging the results of all the experiments of each kind on two animals.

rate of emptying at any time was not significantly affected by the experimental conditions. There is no evidence in these results that the initial emptying was accelerated by keeping the pylorus open. The delay in the emptying of olive oil when the pylorus was kept open was evident during all phases of the emptying process.

The emptying curve has a characteristic appearance for each substance, suggesting differences in their effect on the mechanism for regulating emptying. For example, the rate of emptying of acid was fairly uniform, the corresponding curve tending to approximate a straight line; the emptying of glucose was rapid during the first ten minutes and then became slower. These results may be explained by the assumption that

tube within the duodenum. The rubber tube attached to the duodenal end of this apparatus was perforated with a number of large holes so placed as to be as near the pylorus as possible. A rather long drainage tube was used, so that when it became filled with fluid a negative pressure of about 30 cm. of water was maintained within its lumen at the upper end. The pylorus was functioning. The gastric contents emptied around the apparatus and drained to the outside without coming in contact with more than a small part of the duodenal mucosa.

Under these conditions 300 c.c. of normal saline left the stomach in an average time of four minutes for one animal and 6.5 minutes for the other. The average emptying times of N/20 HCl were five and eleven

minutes for the two animals respectively; for olive oil they were eight and 15 minutes. If anything went wrong with the drainage—for example if the negative pressure was not maintained—the emptying of oil was much delayed. In one experiment, in which the appearance of bile in the drain tube indicated that some oil was free in the duodenum, there was no appreciable emptying of oil from the stomach for more than one hour.

Considering the fact that contact of the material with the intestinal mucosa could not be prevented completely even by drainage under negative pressure, we think that the slight differences in emptying time recorded with the duodenum draining can be disregarded, and the conclusion maintained that the differences in emptying time observed under normal conditions were entirely the result of stimuli acting within the intestine.

The experiments with duodenal drainage show that even normal saline has some effect within the intestine, tending to delay the emptying of the stomach, since duodenal drainage reduced the saline emptying time to about one-fourth of that required normally.

Certain incidental observations seem worth recording. Bile was found at some time in the gastric contents regularly after alcohol, acid or olive oil had been given. This was true whether or not the pylorus was able to function. It appeared earlier and in greater abundance when the pylorus was kept open. The greatest amount of regurgitation occurred after oil, and the next greatest after alcohol. With both substances there were frequent increases in the amount of the gastric contents. We got the impression that the normal mechanism of fat digestion may involve the passage of the fat into the duodenum to be mixed with the digestive secretions and its later return to the stomach for storage during the process of digestion.

In the beginning we attempted to use Wesson oil as a fatty substance. We were unable to do so because the animals consistently vomited the Wesson oil, although they tolerated equal amounts of olive oil fairly well. The olive oil was occasionally vomited—more frequently when the pylorus was kept open.

In the experiments with alcohol, the animals presented gross evidence of intoxication only when the stomach emptied rapidly. We infer from this that the rapid absorption of dilute alcohol, such as to produce intoxication, takes place from the intestine rather than the stomach.

In one animal the rapid passage of alcohol into the duodenum brought on fits of sneezing. We have noted a similar reaction in another animal in which any mechanical irritation of the duodenum caused sneezing.

DISCUSSION

The stomach can empty only when its contents are subjected to a force sufficient to overcome the resistance to their passage into the duodenum. The force is provided by peristalsis in the antrum or increase in the tone of the gastric muscle as a whole, and takes the form of pressure on the contents, especially in the region of the pylorus. The resistance encountered is due either to the narrow pylorus or to back pressure from within the duodenum, and is determined quantitatively by the activity of the sphincter or the duodenal muscle respectively. There are therefore three mechanisms available for the regulation of gastric emptying, either separately or in combination: (1) variations in the tone or the peristaltic activity of the gastric muscle; (2) opening and closing of the pylorus; (3) variations in the activity of the duodenal muscle. Which of the three is most important in the regulation of gastric emptying under normal circumstances remains undecided, although there has been in the past a tendency to center attention on the pylorus.

The results here reported, which are in accord with the evidence available from the literature, demonstrate that the pylorus is not an esential part of the mechanism that regulates the emptying of certain liquids, including some believed to be of the greatest importance normally as stimuli for the regulatory mechanism.

Our results do not show an acceleration of the initial emptying rate with the pylorus open, although such a change appears to be a constant result of surgical removal of the pylorus. This difference may be due to the fact that the first observation in each of our experiments was made too late to detect the more rapid initial emptying when it occurred. It is more probably an indication that the materials which we used contained nothing capable of retarding initial emptying, so that this phase was comparatively rapid even in the controls. Any delay in initial emptying is evidently due to stimuli which act within the stomach. In selecting our materials for investigation, we chose those which are thought to delay evacuation only when present in the duodenum or other part of the intestine. It is in regard to the significance of the effect on the pylorus of duodenal stimulation that there has been the greatest difference of opinion.

The actual cause of the slower emptying from the stomach of such substances as we used can, perhaps, be determined by measuring simultaneously the intragastric pressure, pressure within the duodenum, and pyloric tone. We have done some experiments along this line which we hope to report at a later time. At present we can say that the function that we have found to vary most consistently with the rate of emptying is antral peristalsis.

The greater delay in the emptying of fat when the pylorus was kept open, as compared to the control experiments, appeared to us to be due to more frequent and extensive regurgitation from the duodenum under these conditions. A similar factor was probably operative in the experiments with alcohol, although it was not great enough to produce an unequivocal difference in the average emptying times; it is slightly suggested also in the results of experiments with acid. Probably one important function of the pylorus is to control duodenal regurgitation. The powerful pyloric contraction which follows each gastric peristaltic wave and coincides in time with an increase in duodenal activity (22) is strongly suggestive of such a function.

Our results show that the gastric contents, though liquid, will not leave the stomach even through a wide open outlet except at a certain rate characteristic for the substance concerned. Therefore the pylorus is not necessary to keep the stomach from "leaking" when its contents are fluid. This fact supports the conception of intra-abdominal mechanics set forth by Cannon (23, 18). He explained that the full stomach is essentially in the situation of a bag full of water suspended in water and will, therefore, not empty by simple drainage due to gravity.

SUMMARY

The emptying time of the dog's stomach for normal saline, isotonic glucose solution, N/20 HCl, 10 per cent alcohol or olive oil was not shortened by the presence of a device which kept the pylorus continuously open.

The rate of emptying of these substances was not accelerated in any observed phase of the emptying process by keeping the pylorus open.

The exit of olive oil from the stomach was retarded throughout the period of emptying and the emptying time prolonged when the pylorus was kept open.

An open pylorus favors regurgitation from the duodenum.

CONCLUSIONS

Closure of the pylorus is not an essential factor in the delayed emptying from the stomach of oil, acid solutions and certain other liquids. One function of the pylorus is to control duodenal regurgitation.

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Duodenal Intussusception*

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DUODENAL intussusception occurs so infrequently that in most textbooks it is not mentioned and Fitzwilliams (1) in his report of one thousand cases of intussusception found no case originating in the duodenum. He further states that "the duodenum, on account of its fixity, is never the starting point of the trouble." However, Kellogg (2) in his excellent book, "The Duodenum," devotes a chapter to duodenal intussusception and reports eleven cases gathered from the literature during the past hundred years. Of these, five originated in the stomach, thus leaving only six of true duodenal intussusception.

After a careful search of the literature we have been unable to find any additional cases. Because of the infrequency of the lesion, the diagnostic problems presented, and its amenability to treatment, we have felt justified in briefly reviewing the earlier cases and in reporting a recent case from the Stanford Medical Service.

CASE REPORTS

Case I: 1830. K. Sundelin (3). Male, aged 47. Always well up to six months before admission. During this period he was troubled with intermittent attacks of severe abdominal pain associated with vomiting. His last attack started after a heavy meal with pains in the lower addomen followed by vomiting. The pains increased in severity, the vomiting persisted, and became "coffee-ground-like," he was thirsty, the extremities were cold, the face was livid, the pulse was rapid and feeble, and there was hyperaesthesia of the abdomen. Autopsy revealed an intussusception of almost the entire length of the duodenum into the jejunum. Directly above the invagination, the duodenum was seen constricted for about two-thirds of its diameter by a smooth solid induration.

Case II: 1866. V. Paris (4). Male, aged 25. About ten months before his fatal illness, he began to notice a heavy feeling in the epigastrium which had no relation to meals. This symptom continued and about five months later was associated with vomiting. Vomitus was not remarkable. Attacks occurred three or four times per week. The patient was not incapacitated. Constipation progressively increased. Nine months later, the attacks increased in frequency and duration. He entered the hospital because of pain and vomiting. On entry, he had no fever, was pale and emaciated, but in no extreme distress. There was pain in the epigastrium and left hypochondrium. His attacks continued irregularly for a period of weeks. He had no relief, became very weak, and died of pulmonary complications. Autopsy revealed a partial invagination of the terminal portion of the duodenum into itself. Only one portion of the circumference of the duodenal wall was invaginated. A fibro-muscular polyp was found which had this portion of the wall for its base.

Case III: 1896. W. Collier (5). Male, aged 21. His illness began about twelve months previous to his admission with pain across the upper abdomen and vomiting. These symptoms increased in severity during the last six months. The pain was not affected by food and the vomitus was not remarkable. On entry, the patient looked anxious

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TABLE I

Summary of the findings in the seven cases of duodenal intussusception

Case	Age	Sex	Symptoms and Signs						Laboratory Findings			Treatment	Outcome	Pathological Report
			Duration	Vomiting	Pain	Weakness	Weight Loss	Tumor	Anemia	Blood in Stool	X-ray			
1	47	M	6 mos.	+	+	+						Medical	Died	Constricted duodenum
2	25	M	10 mos.	+	+	+						Medical	Died	Fibromyoma for polypus
3	21	M	12 mos.	+	+			+				Surgical	Died	Polypi
4	75	F											Cadaver	Fibroadenoma
5	69	M	4 mos.	+	0	+	+		+	+	Dilation of duodenum and upper jejunum	Surgical	Recovered	Benign adenoma
6	58	M	12 mos.	+	+	+		0		+	Dilated duodenum	Medical	Died	Mucus adenoma
7	62	F	9 mos.	+	0	+	+	+	+	+		Surgical	Recovered	Papilloma

and decidedly ill. Nothing was discovered in the abdomen to account for the pain and vomiting. His symptoms continued relentlessly under conservative regimen. One evening, the patient was seized with more severe abdominal pain and urgent vomiting. Later, a distinct mass could be made out, running obliquely across the abdomen from left to right. Surgery was advised with the tentative diagnosis of intussusception. A large insussusception was found commencing within a few inches of the pylorus. The invagination was easily reduced but his condition did not improve. On postmortem examination an enormous number of polypi were found. These varied in size from a pigeon's egg to a pea and were scattered throughout the stomach and the small intestines with the greatest number in the duodenum and the upper jejunum. The specimen showed a large lobulated villous growth situated in the duodenum a short distance from the pylorus. The constricted attachment of this villous growth to the mucous membrane was the starting point of the intussusception.

Case IV: 1897. P. Thompson (6). Female cadaver, aged 75. The author states, "I was able to ascertain that for some months before death there had been no gastric disturbance and no symptoms to lead one to suspect the presence of the growth." The cause of death was certified as "senile decay." Examination of the intussusception revealed that the pylorus and the first part of the duodenum had passed into the second part of the duodenum and formed a prominent mass from which the pedicle of the tumor projected. The tumor pedicle originated from the inferior margin of the pyloric ring. Microscopic diagnosis of the tumor was "fibroadenoma."

Case V: 1926. E. L. Kellogg (7). Male, aged 69. Family and past history were non-contributory. For the past four years, he had noted periods of fullness and flatulence but no marked symptoms until August, 1926. At that time, he had a sudden attack of nausea and vomiting followed by severe cramp-like pain, lasting ten to twenty minutes and recurring at frequent intervals for twenty-four hours, located below the navel and extending across the abdomen. The symptoms disappeared after three days and he remained well until October, 1926, when he vomited repeatedly without pain. Later in the same month there was slight fever for three days and for two days the bowels did not move. This was followed by a gradual loss of weight and strength and progressive anemia. In November, following an attack of vomiting with marked prostration, he was admitted to the Polyclinic Hospital. He was moderately nourished but very anemic. The pulse was rapid and feeble, there was slight tenderness to pressure about the navel, and the bowels moved with anemata. Roentgen-ray investigation showed dilatation of the duodenum and upper jejunum. This was attributed to adhesions causing obstruction. The stools contained occult blood. At operation, the upper portion of the jejunum was distended, dark, and contained a solid oval mass which was movable within the lumen. This was pushed upward through the jejunum and the duodenum until it presented at the pylorus but could not be forced past the pyloric ring. It was readily delivered through an incision crossing the pylorus at right angles and proved to be a pedunculated tumor attached to the posterior duodenal wall close to the pyloric ring. The tumor was removed and the wound closed without drainage.

It was determined that the superior duodenal angle had been obliterated by stretching of the hepatoduodenal ligament, and that an intussusception of the duodenum and pyloric end of the stomach into the jejunum had taken place without causing complete obstruction.

Pathologist's report: Tumor from the duodenum: adenoma, benign.

Follow-up reports indicated that within about six weeks his blood picture was practically normal. He was rapidly gaining weight. Three years later he was in good health.

Case VI: 1929. L. Muller (8). Male bartender, aged 58. Patient entered the clinic with the symptoms of pyloric stenosis with gastric dilatation which was thought to be the result of a cancer or ulcerated cicatrix. For the past

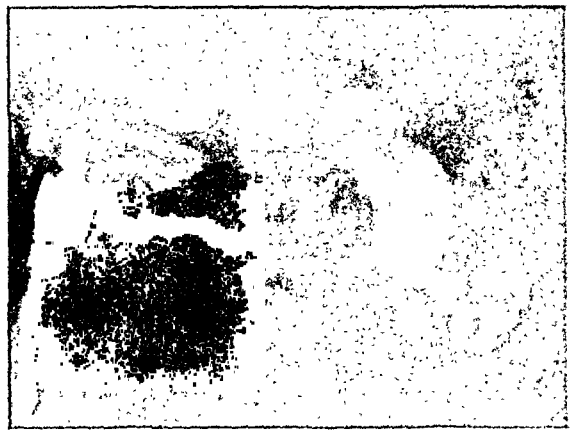


Fig. 1. Case VII. Barium examination showing dilated duodenum with cone-shaped distal end.



Fig. 2. Case VII. Barium examination at three and one-half hours; stomach and duodenum still filled with barium.

year, he had experienced frequent vomiting and severe thirst. The vomitus was usually of a mucous nature. Four weeks before hospital entry, pain appeared in the right side. He vomited after each meal and complained of anorexia, weakness, and frequent fainting spells. His urine volume was small. He had no fever. He continued working until eight days previous to admission.

On physical examination, he appeared extremely emaciated and vomited frequently. The vomitus was bloody mucus with no fermented odor. No masses were felt in the abdomen. Benzidine reaction in the stool was triple plus. On the second day, he had a little muscle spasm but nothing definite could be made out to explain his complaint. Patient failed rapidly and died on the third day.

At autopsy, the stomach was in its usual position. About four finger-breadths below the pylorus near the superior duodenal angle a five-centimeter piece of the upper outer circumference of the duodenal wall disappeared into a funnel-like lumen. At the apex was found a walnut-shaped soft, purple polyp which was covered with fine villi. The polyp was rich with blood but was not ulcerated or hemorrhagic. Nothing remarkable was found in the rest of the duodenum except adhesions between it and the liver capsule. The jejunum was enlarged twice its normal size for the first meter portion. In the enlarged portion, there were two more invaginations; one, about a hands-breadth below the duodeno-jejunal junction and the other twenty-five centimeters further down. The former was isoperistaltic and circular and the latter was antiperistaltic and retrograde. The ileal contents were of a black, tarry-like nature.

Histological examination: The polyp was a mucous adenoma of papillary character.

Case VII: Stanford. 1936. Mrs. B. T. Female, aged 62. Entered Stanford Hospital August 28, 1935, stating she had been perfectly well up to December, 1934, at which time she began to be troubled with nausea and vomiting, the latter coming on fifteen minutes to two hours after meals. She felt that in the last six months she had vomited practically all the food eaten. Her weight had dropped from two hundred to ninety-six pounds at the time of admission. For several weeks before admission the vomitus had been coffee-ground-like in character, there had been extreme weakness, there had been no pain, and stools had been tarry.

The family and past history was unimportant.

Physical examination, made by a student at time of admission, was unimportant except for the evidence of emaciation and the presence of a large mass in the epigastrium. Later, examination by the medical house officer, failed to confirm the presence of this mass. A few days later, the mass was again described about fifteen by ten centimeters in the epigastrium to the right of the midline. It was noted that this mass could be pushed across the midline.

A blood count showed 3,750,000 red cells with a hemoglobin of 67%; white and differential count was unimportant.

A urinalysis was negative.

A histamine test-meal showed a maximum total acidity of twenty-four; free hydrochloric of eight; a strong occult blood reaction, highest ten minute volume was twenty-five cubic centimeters.

An icterus index was fifteen.

Stool examination was strongly positive for blood.

Blood Wassermann was negative.

A gastro-intestinal X-ray series on August twenty-ninth was first reported to show no demonstrable disease of the gastro-intestinal tract. After further consultation with the X-ray department, the following report was given: "Preliminary film of the abdomen shows no abnormal small or large bowel gas. No calcified or soft tumors are seen. Examination of the stomach with barium shows a normal appearing stomach. Peristaltic waves travel to the end of the stomach. The duodenal cap fills completely. Barium gets into the duodenum but at the immediate examination no barium at all passed through the duodenal loop. The obstructed end of the duodenum is cone-shaped. The patient was seen again in three and one-half hours at which time the barium was still in the stomach, and in the duodenal loop. Only a tiny amount of barium had passed into the jejunum. At twenty-four hours, the stomach and small bowel were empty. *Conclusion:* Obstruction in the duodenum. This was complete for a few hours but later the obstruction was apparently relieved for at the twenty-four hour examination the stomach and duodenal loop were both empty."

On September third, examinations made by Dr. A. L. Bloomfield who was unable to feel any abdominal mass. The following day, patient had slight fever and swelling of the left parotid. Vomiting persisted. Dr. E. Holman was called in in surgical consultation at which time no abdominal mass was palpated. Diagnosis was deferred. Patient kept up symptomatic treatment. On September eighth, patient was again seen by Dr. Bloomfield who reported "the whole situation is still obscure, tongue is definitely smooth, abdomen is very soft, and I am still unable to feel any mass. The story of poor diet may be related to the present anemia and glossitis."

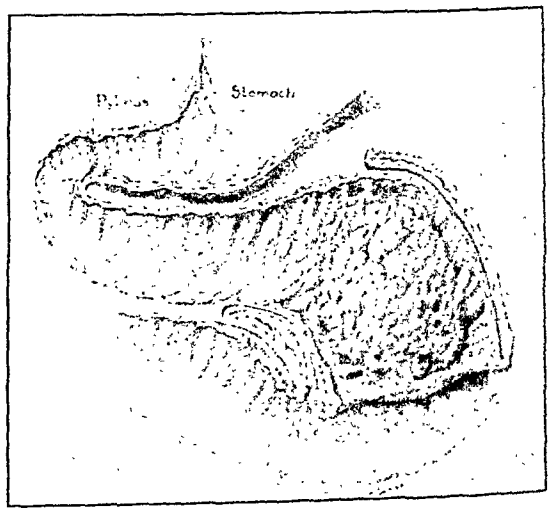


Fig. 3. Case VII. Drawing showing the papilloma in the duodenum and the intussusception.

is generally thought to be stasis of bile with secondary infection playing a minor role. The diagnosis of gall bladder disease depends primarily upon roentgenologic findings. This will reveal failure of the gall bladder to concentrate the dye, failure of the dye to reach the gall bladder, or a deficient secretion of bile, all of which will show non-visualization of the gall bladder.

The author believes that the treatment should attempt to relieve bile stasis. In accordance with this, one of the authors began giving a diet of cream, butter and in some cases eggs, plus frequent feedings of high smooth bulk together with antispasmodics. Cooked fats or greases were curtailed. During the last three years keto-cholanic acids were also used. The author believes that this method results in a direct stimulation to the flow of liver bile and also initiates contraction of the gall bladder.

The results of this therapy on 131 patients showed that those receiving the keto-cholanic acids were improved greatly both subjectively and objectively, except in those cases where large stones were demonstrated. These cases, however, showed marked subjective improvement. The authors conclude that this is the therapy of choice in low grade gall bladder disease, but that it should not be used in common duct obstruction and acute cholecystitis.

Francis D. Murphy, Milwaukee.

SCHINDLER, RUDOLF, ORTMAYER, MARIE AND RENSHAW, JOHN F.

Chronic Gastritis. J. A. M. A., Vol. 108, p. 465, Feb. 6, 1937.

Chronic inflammation of the stomach, although not considered an entity for the past thirty years, has recently been shown to exist. Clinically chronic gastritis was rediscovered with gastroscopy by the senior author in 1922. The normal mucosa has been studied in people of all ages and has been found to be smooth, silk-like, glistening and orange red.

In 2500 patients with abdominal complaints who were examined gastroscopically, 50 per cent present evidence of mucosal changes characterized by layers of whitish, grayish or greenish mucus, or hyperemic spots. These were termed superficial gastritis and usually healed. Other cases showed greenish gray spots which did not change and were termed atrophic gastritis. In still others, the mucous membrane was swollen, thickened, velvety, often containing hemorrhages, and erosions and nodules, nodes, creases or crevasses. This was termed hypertrophic gastritis and in spite of careful treatment would not return to normal. The fourth type occurs postoperatively, consists of all other three forms combined and has the worst prognosis.

In a study of 228 cases at the University of Chicago, it was found that the age varied from twenty to sixty years. The duration of symptoms averaged five and one-half years. The hypertrophic form was commonest in the male, the other forms equally distributed. In some cases appetite was poor, in others normal. The distress was epigastric, delayed in the hypertrophic form, and occurring shortly after meals in the atrophic form. Periodicity was present in some of the hypertrophic forms, but not as marked as in ulcer. Many had gas and belching.

In all forms the intestinal function was normal.

Physical examination was usually negative. In some cases there is a tender zone on light palpation below and to the left of the navel. Gastric analysis is practically useless. X-ray examination also is of little help in diagnosis. Gastroscopy is the only diagnostic procedure at present.

The treatment consists of a very bland diet, fed in frequent small amounts. Raw fruits and vegetables must be avoided. Bed rest for eight days and hot applications should be used in the superficial form. Lavages



AN IMPORTANT FACTOR

The intestinal tract, in the opinion of many authorities, constitutes one of the most important factors in systemic disease. So frequently is it the focus of infection that it can no longer be overlooked in the etiology of many systemic disorders, allergic and otherwise.

When symptoms point definitely to the absorption of toxic substances from the intestinal tract, consider the value of Soricin (sodium ricinoleate) as a detoxifying agent. Soricin inhibits putrefaction and proteolysis, and tends to reduce toxicity of the bowel content.

Thus, the absorption of toxic substances from the bowel—evidenced by such, frequently remote, symptoms as migraine, vertigo, and urticaria—can be checked in many cases by the oral administration of Soricin.

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10 grain size, available in boxes of 20 and 100 capsules each.

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the lumen, giving rise to slowly developing obstruction."

It would thus seem difficult to differentiate the symptoms arising from primary tumor with obstruction from those arising from tumor complicated by intussusception, except that the symptoms of obstruction from tumor would probably be more constant than those from intussusception. An evanescent mass is probably the most typical finding. Treatment is obviously surgical and should be successful if complications are not encountered. Naturally, the earlier the diagnosis is established and treatment undertaken, the better the prognosis. The post-operative course in the Stanford case was extremely difficult because of the deficiency states.

CONCLUSIONS

1. True duodenal intussusception does occur but is a rare lesion.
2. It is usually secondary to a benign tumor of the duodenum.
3. It may occur in males or females and from twenty-one to seventy-five years.
4. Vomiting, emaciation, anemia, evanescent epigastric mass, and X-ray evidence of dilatation of the duodenum are the usual findings.
5. Surgical treatment should be successful if complications are not encountered.

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A Study of Peptic Activity by Means of the Double Histamine Test

By

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IT is not our intention to review in detail the voluminous literature on the secretion of pepsin or its rôle in the etiology and chronicity of peptic ulcer, except to state that values for pepsin are usually increased in the presence of peptic ulcer. There also is much evidence to suggest that ulcers heal with great difficulty in a medium of gastric chyme which has an increased peptic concentration. There can scarcely be any doubt that some relationship exists between persistently accentuated peptic activity and accentuated ulcer-forming tendencies in certain cases. In a previous paper we have shown that a remarkable degree of correlation exists between the amount of ferment and the severity and intractability of the symptoms.

Recently, we have made some investigations regarding the behavior of the chief cells and the parietal cells during the course of a double histamine test, which consists of the study of the secretion following two successive injections of histamine. The object of this study was to learn more about the ability of the cells to maintain vigorous secretory rates. We were interested not only in learning how high a concentration of acid and pepsin could be attained but we wanted to know how long the acid-pepsin secretion would be continued before retardation of these rates became evident, for we believed that both the intensity and the duration of the secretory response might serve as a means of determining the accentuated ulcer-producing tendencies in certain cases.

The controversy regarding the ability of histamine to stimulate the secretion of pepsin continues. Most observers have noted an increase in peptic activity of the gastric juice shortly after the injection of histamine, but many have assumed that this is due solely to a washing out of preformed pepsin and that it is not the result of actual stimulation of the parietal cells.

Some interesting facts regarding the behavior of the parietal cells during the course of the double histamine test were observed. These suggested that stimulation of the parietal cells by histamine results in a copious outflow of pepsin from the tubules in much greater amounts than could be expected from a simple washing-out process.

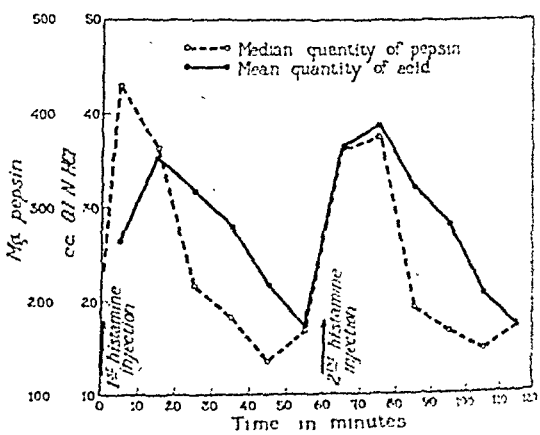


Fig. 1. Change in the secretion of pepsin and gastric acid following the injection of histamine; one may note a marked rise in the secretion of both constituents following the second injection.

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Submitted March 17, 1937.

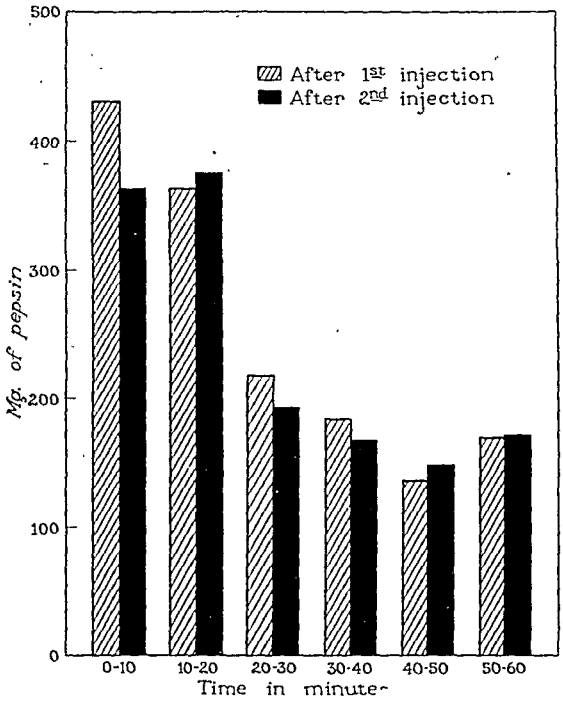


Fig. 2. Comparison of increase in the secretion of pepsin following first injection of histamine and that following a second injection; the increase produced by the second injection is equal to that produced by the first.

METHOD OF STUDY

In performing double histamine tests a small-bore Sawyer tube was introduced into the stomach and the gastric contents were aspirated as completely as possible. The contents then were evacuated at ten-minute periods during which time unstimulated fasting secretion was removed. After collecting two or three fasting specimens and assuring ourselves that the stomach was free of secretion, histamine was injected subcutaneously in doses of 0.1 mg. for each 10 kg. of body weight. Following this, gastric juice was aspirated for six periods of ten minutes each. Then the same amount of histamine was again injected subcutaneously and specimens were collected for six more periods of ten minutes each. The concentration of pepsin was estimated by the modification of the Gilman-Cowgill method described by Osterberg, Vanzant and Alvarez and acidity was determined by titration with tenth normal solution of sodium hydroxide, using Töpfer's reagent as an indicator. Figures representing quantities of acid and pepsin secreted for each period of ten minutes were obtained by multiplying the concentration of the substances by the volume of the specimen.

RESULTS

This test was performed in sixty-six cases. In a large number of these cases the patients had peptic ulcer. Table I shows the concentration and quantity of the pepsin secreted during the successive ten-minute periods.

From a study of the results obtained in these cases it is evident that the argument, that the secretion of pepsin is not stimulated by histamine but that preformed pepsin is merely washed out, breaks down because the shortness of the interval between the two injections precludes the possibility of pepsin accumulating in the tubules in as large a quantity as we obtained following the second injection of histamine. The curves (Figs. 1 and 2) show that the secretion of pepsin reaches its height in the first twenty minutes after injection and then falls rather abruptly to a low level. Following the second injection of histamine, an almost identical curve was observed except that

TABLE I

The mean and median concentration and quantities of acid and pepsin secreted by sixty-six patients

Time after first dose of histamine, minutes	Free hydrochloric acid				Pepsin			
	Concentration		Quantity		Concentration		Quantity	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
0					881	557		
10	62.0	65.0	26.4	26.9	1523	1100	485	430
20	82.2	87.1	35.3	33.6	1313	1000	408	364
30	86.8	91.0	31.7	28.1	972	738	225	217
40	80.0	85.0	28.0	27.9	969	637	214	183
50	66.3	69.4	21.8	15.7	792	549	175	136
60 Second dose of histamine	59.4	62.7	17.3	11.9	880	650	141	169
70	72.6	74.0	36.4	26.2	1297	1032	382	363
80	85.5	92.9	38.7	34.4	1220	930	400	375
90	85.7	86.7	32.1	28.0	954	750	242	192
100	79.5	83.0	28.0	22.3	847	660	219	167
110	66.4	71.7	20.6	16.3	824	640	182	147
120	62.8	64.3	17.0	12.4	970	836	178	171

slightly higher values for pepsin were obtained in the first ten minutes after the first injection than were obtained in the corresponding period after the second injection. This difference may well be due to a washing out of preformed pepsin by the first injection.

SUMMARY

It would seem that histamine performs two functions so far as the presence of pepsin in the stomach is concerned: First, it causes a washing out of the preformed pepsin and, second, it stimulates an actual secretory increase in the function of the parietal cells.

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The Effect of the Oral Administration of Bile Salts on the Composition of Human Fistula Bile*

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THE enterohepatic circulation of bile acids as postulated by Schiff (1) in 1870 has since been confirmed and proved conclusively by the work of numerous other investigators (2, 3). Although the changes occurring in the enteric portion of this circulation are well known, the intrahepatic mechanism has remained an unknown factor. However, by observing the changes in the chemical composition of the bile, it is possible to determine the end results of the bile acid metabolism as it is effected by both the endogenous and exogenous factors involved in the enterohepatic circulation of bile salts.

Whipple and his coworkers (4) have carried out careful and extensive studies on bile acid metabolism in the dog. These workers have shown that the limiting factor in the output of bile acids is the amount of available cholic acid. Although the precursors of cholic acid are as yet not definitely known, Whipple and Smith (5) have shown that tryptophane is essential for the formation of cholic acid.

In the dog Whipple (4) has also observed the importance of diet. The lowest output of bile acids occurred in animals which received only carbohydrates. The output of bile acids was lower on this diet than in the fasting dogs, the reason being that there was less destruction of body protein in the animals on a carbohydrate diet than in the fasting dogs. The highest output was obtained with a meat diet which supplied ample proteins. In the fasting dog the output of bile acid remained at a constant level for a considerable length of time, and this fixed level is called the "endogenous level" (4) of the bile acids. However, Whipple obtained the maximum output of bile acids by bile salt feeding in these dogs. Furthermore, these experiments have demonstrated that there is a regulatory mechanism present in the liver which controls the secretion as well as the destruction of bile acids. The greatest stimulation of this hepatic secretory mechanism can be produced by the administration of bile salts.

Very few similar determinations of the bile salt metabolism have been carried out on human bile. Recently Doubilet (6) has described improved methods for bile salt analysis which are applicable to human bile. We wish to present a series of cases in which we have attempted to determine the components of human bile as they exist in fistula bile obtained from cases of postcholecystostomy and choledochostomy, and further, to observe the changes that can be produced in the composition of that bile by the oral administration of bile salts.

METHODS

The constituents of the fistula bile and the methods used for their determination are as follows: cholic, desoxycholic, and taurocholic acids by the methods of Doubilet (6); total conjugated bile acids by the method of Smith, Groth and Whipple (7); and cholesterol by the method of Elman and Taussig (8).

The human fistula bile used for the following differential chemical analyses was obtained from ten patients who had been operated for some pathology of the biliary tract. In some cases the drainage tubes were placed in the gall bladder and in the remaining cases "T" tubes were placed in the common bile duct. The specimens were collected for periods of 24 hours, and aliquot portions were used for analysis.

All patients were given the same type of diet postoperatively. However, in those patients with severe postoperative nausea and vomiting, the entire diet was not taken and this would cause some variation in the rate of secretion of bile acids.

The hippuric acid test was used to determine the degree of hepatic damage and the serum bilirubin was used to measure the degree of icterus.

Five patients who were used as controls did not receive any bile salts either preoperatively or postoperatively. The remaining five did receive bile salts* during the postoperative period of study.

DISCUSSION AND RESULTS

The first four cases presented in Table I form a control group in that they did not receive any bile salts and they all received the same type of diet, although an accurate record of the food intake was not kept.

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Received January 21, 1935.

*The bile salt preparation used in these studies was 'Bilron' (Iron Bile Salts, Lilly) which was supplied through the courtesy of Eli Lilly and Company.

TABLE I

Differential quantitative analysis of human fistula bile. Control group; did not receive bile salts

Case No.	Post-operative Day	Cholic Acid mg. %	Desoxy-cholic Acid mg. %	Acids Conjugated with Taurine mg. %	Acids Conjugated with Glycine mg. %	Total Bile Acid mg. %	Free Bile Acid mg. %	Cholesterol mg. %
1 Choledochostomy	1	109.5	146.5	335	0	256		68.6
	2	78	88	207	0	166	8	34.3
	3	97.5	53.5	130	93	150		60.9
	4	111	103	158	80	214		70.1
	5	140	106	170	195	246		73.9
	6	190	217	163	335	407		115.9
	7	193	243	171	395	439		136.9
	8	209	173.5	171	450	382		109.1
	9	204.5	110.5	261	332	314		146.4
	10	184	98.2	139	330	282		159.3
2 Choledochostomy	11	225	85	152	407	311		69
	12	244	204	186	349	448		67
	13	160	177	149	145	337		60
	14	144	141	143	146	286		43
	15	147	97	149	154	245		37
	17	194	244			439		60
3 Cholecystic fistula	1	113	307			420		48
	2, 3, 4	173	829			1003		35
	5	162	467			629		34
	6	177	426			603		59
	7	242	352			594		55
	8	227	362			589		44
	9, 10, 11	227	343			571		48
4 Cholecystic fistula	2, 3	90.4	309			399		90.5
	6	194	172			366		156
5 Choledoch-ostomy (died)—	1	210	107	147	271	318		43
	2	43	39	175	33	84		25
	3	22	0			22		12

In Case 1 the collection of bile was begun immediately after surgery, but in Case 2 the collection of specimens was not started until the eleventh day after surgery. Together these cases present a complete daily analysis of human choledochal bile over a period of 17 days. The results indicate that the composition of this bile and the proportion of each component studied in the 24 hour specimens is remarkably uniform in spite of the variable diet. Similar results have been reported by Whipple and Smith (9) in their analyses made on dog bile under similar conditions.

In Cases 1 and 2 and in other cases of this series the output of conjugated bile acids, as determined by the *amino-nitrogen method*, was often found to be larger than the output of total bile acids as determined by the iron method. Similar results were also observed by Doubilet (10) in his postoperative fistula cases. His explanation of this is that the fistula bile may contain other amino-nitrogenous materials which are soluble in alcohol thereby increasing the concentration of the conjugated acids above that of the total bile acids.

The bile cholesterol output in these cases was similar to the amount found in fistula bile by Wilkinson (11).

The third case in the group differs from other cases in that there was a higher proportion of desoxycholic acid, although the amount of cholic acid and cholesterol was at the same level observed in the first two cases. The conjugated forms of bile acids were not determined in this case. On the fourth day there was a sudden and unexplainable rise in the desoxycholic content of the bile, while in the other cases this immediate postoperative period was characterized by a decreased output of all bile acids and cholesterol. However, this rise was of short duration so that on the eleventh day the amount of desoxycholic acid present in the bile approached the amount found in the other control cases. The cholic acid and cholesterol content followed the same course as outlined in the first two cases.

The fourth case in this group was that of a cholecystic fistula and the specimens were obtained on the second and the sixth days. The composition of the bile in these specimens was the same as that observed on the same days in other cases of this control group.

The fifth case demonstrates the changes which occur early in the course of "hepatic insufficiency." The specimen of the first 24 hour period after surgery showed a level of bile acids and cholesterol similar to that found in the other cases in the first postoperative specimen. In the second and third specimens there was a very rapid decline in the concentration of these substances in the bile. This decrease in the quantitative secretion of bile acids and cholesterol was not paralleled by a proportionate decrease in the volume of bile obtained from the fistula. The volume of the first specimen was 153 c.c.; the second was 660 c.c.; and the third was 163 c.c. The patient died a few hours after the third specimen was obtained.

Smyth and Whipple (12) have observed a similar phenomenum in dogs. When the dog was given a small dose of a hepatotoxic drug such as chloroform, it was possible to reduce the bile acid content of the bile to within 10 per cent of normal without decreasing the flow of bile. Furthermore, it was found that there was no change in the microscopic appearance of the liver cell in the dogs which had received this dose of chloroform although there had been a marked change in the metabolic function of the liver cell. Bollman and Mann (13) have been able to produce the opposite result in dogs by means of toluylenediamine. After

TABLE II

Differential quantitative analysis of human fistula bile. This group received bile salts

Case No.	Post-operative Day	Cholic Acid mg. %	Desoxy-cholic Acid mg. %	Acids Conjugated with Taurine mg. %	Acids Conjugated with Glycine mg. %	Total Bile Acid mg. %	Free Bile Acid mg. %	Choles-terol mg. %	Iron Bile Salts cm./day
6 Choledoch-ostomy	1, 2	61	91.3	134	198	152		67	0
	4	2-4.5	37.8	216	407	323		62	1
	6	449.5	209	216	856	759		101	1
	7, 8	449.5	377	297	269	827	261	135	1
	11	526.5	503	358		1029		114	1
	13	519.5	383	321	823	902		108	1
	14	544	178	259	1151	722		130	1
7 Cholecystos-tomy	G. B. bile	373	2354	184	1984	2028	760	109	0
	Fist. bile	39	350	69	334	390			0
	1	172	399	189	542	572			1
	2	360	346	114	740	706			2
	3, 4, 5	338	367	69	995	705			2
	6	337	371	126	876	708			2
	7	221	1528		805	1752	947		2
	8	355	1536	41	1159	1914			2
8 Choledoch-ostomy	1	85	341	141	113	425	171	86	0
	3	52	216	131	120	262	11	60	0
	4	34	123	117		157	40	50	0
	6	125	209	139	100	337	98	115	0
	7	79	481	81	80	560	390	76	0
	8	78	274	66	98	353	189	66	0
	9	123	131	95	160	255		81	0
	11, 12	286	385	147	441	672	84	168	2
	13	482	490			972		156	2
9 Cholecystic fistula	1	69	122	127	128	192		72	0
	2	29	51	69	144	80		30	0
	3	31.4	74	118	81	105		27	0
	4	272	249	294	209	521	10	119	0
	5	402	212	225	592	614		123	2
	6	496	231	287	948	727		150	2

the administration of this substance to dogs, a marked suppression of the flow of bile occurred, but a rise in the bile acid content of the peripheral blood and urine indicated that there had not been an equal depression of the bile acid formation by the liver. These results would indicate that the formation of the bile acids by the hepatic cell is not merely a mechanical filtration of these substances from the portal blood but rather is a distinct metabolic function of the liver cell.

The four cases presented in Table II received bile salts during the postoperative period. The first case in this table (Case 6) received bile salts from the third to the fourteenth day. The administration of bile salts produced a marked increase in the amount of cholic acid and desoxycholic acid and in the amount of bile acids conjugated with glycine, but there was no definite change in the amount conjugated with taurine or in the amount of cholesterol contained in these specimens of bile. The increase in bile acid elimination occurred in the first 24 hour specimen after administration of the bile salts, and the bile acid content was maintained at this high level for the remainder of the period of observation. This level was distinctly higher than any observed in the control cases during a similar period of observation.

At the time of operation of Case 7, sufficient bile was found in the gall bladder to permit a complete analysis of this bile. These results are given in Table II. This patient had received bile salts for 1 month prior to operation, but this medication had been discontinued for 10 days before surgery. This sample of gall bladder bile differed from the fistula bile studied in that the bile acid content was very much higher and this increase was confined chiefly to the desoxycholic acid fraction and the portion conjugated with glycine. Taurine and cholic acid and cholesterol were not increased above the amount found in the fistula bile in the same case after surgery. There was also a large amount of free bile acid present in this specimen. This relative reduction of the cholic acid content and the presence of free bile acid was observed by Doubilet (10) in gall bladder bile from cases of cholecystitis. Doubilet considers these findings significant of cholecystitis and he is of the opinion that the inflamed gall bladder is unable to absorb the desoxycholic and the free bile acid. The pathological report of the gall bladder obtained from Case 7 showed a definite chronic cholecystitis. The cholesterol content of the gall bladder bile was not increased above the amount found in the fistula bile.

Further study of the specimens of fistula bile obtained from Case 7 after the choledochostomy revealed a marked decrease in the bile acid content during the first 48 hours after surgery. This depression of bile acid secretion was observed during the immediate postoperative period in the other cases in this study, and Greene, Aldrich and Rowntree (14) have observed the same decrease in bile acid output in the dog after a cholecystectomy under iso-amyl ethyl barbituric acid narcosis. This depressant effect of surgery of the extrahepatic biliary system may have been due to the operative procedure itself, the anesthetic, or a disturbance in the portal circulation.

The administration of bile salts was started in Case 7 during the first 24 hours after surgery, and the output of bile acids promptly rose to a level above that observed in the control cases. The cholic acid showed less response than the desoxycholic acid to the oral administration of bile salts. During the eleventh day there was a very great increase in the amount of desoxycholic acid secreted. Again, as in all of the other

TABLE III

Hepatitis treated with bile salts (Case 10)

Post-operative Day	Cholic Acid mg. %	Desoxy-cholic Acid mg. %	Acids Conjugated with Taurine mg. %	Acids Conjugated with Glycine mg. %	Total Bile Acid mg. %	Free Bile Acid mg. %	Choles-terol mg. %	Serum Bili-rubin mg. %	Food Intake Calories	Iron Bile Salts gm./day	Volume of Bile c.c.
8	0	0	82	0	0		0			0	440
9	0	0	91	0	0		0	4.7		0	540
10	0	0	72	14	0		0			0	885
11	0	0	111	0	0		0		889	0	163
12	31.5	0	131	0	0		0		985	2	285
13	54.5	30	108	0	84		0		1103	2	560
14	127.5	120	156	167	247		9.1	4.7	794	2	182
16	70.5	128	86	126	199		10.32		747	2	550
17	80	110	111	152	190		11	2.1		2	615
18	78	83	197	15	161		12		1120	2	770
19	53	287	90	38	340	212	9	1.9	1219	3	1250
20	37	452	123	0	490	402	6		1236	3	1170
21	79	54	143	63	132		12		1301	3	1300
22	62	37	114	23	99		8		1048	3	
23	89	35	169	83	124		12		1469	3	
24	134	86	163	169	220		11		1584	3	
25	182	73	175	255	255		14	Trace	1585	3	
26	253	209	179	392	462		22		1417	3	
27	131	92	155	130	223		6		1440	3	
28	163	52	151	285	215		21		1523	4	
29	73	109	126	45	183	12	14		1695	4	
30—33	76	365	147	0	441	299	30			4	
34—39	136	261	94	—	397		30			4	

cases, the cholesterol and taurine fractions were only slightly affected by the bile salt administration.

In the two remaining cases in this table the bile salts were not started until much later in the post-operative period. The decrease in the bile acid and cholesterol content of the bile during the first few days after surgery was very evident in these cases (Cases 8 and 9). In both patients the composition of the fistula bile prior to the administration of bile salts was very similar to that observed in the control cases presented in Table I. The bile salts produced a rise in the cholic, desoxycholic, and bile acids conjugated with glycine, but produced no definite change in the acids conjugated with taurine or in the cholesterol output.

Case 8 differed from all others in this study in that all specimens of the bile contained free bile acid, while in the other cases free bile acid was found only occasionally.

Case 10 is presented in Table III. In this patient the pathology was found to be intrahepatic rather than extrahepatic. Grossly, at the time of operation, the liver presented the typical picture of a severe hepatitis. It was possible in this instance to measure the exact amount of food taken by the patient. The stools were examined for urobilin and bile salts. The urine was tested for bile salts and the degree of icterus was followed by means of the serum bilirubin test.

The patient's condition was critical for the first 8 days after surgery and it was doubtful if he would survive. Several transfusions were necessary as well as intravenous glucose solution during the first portion of the postoperative period. When the collection of bile was begun on the eighth day it was impossible to detect any cholic acid, desoxycholic acid, or cholesterol in the bile. Some taurine was found, but a portion of this may have been due to the presence of ethereal sulphates or sulphur compounds in the bile other than taurine. It is of interest that this patient was able to survive with the hepatic function at such a very low ebb for 12 days. These results are similar to those reported by Ravdin and his associates (15), who found that bile salts were always absent in the liver bile after the common duct had been completely obstructed for a week or more and that their reappearance occurred only after a considerable time. Furthermore, Greene, Walters, and Frederickson (16) observed that in cases with hepatic injury due to biliary cirrhosis there was a delayed reappearance of bile salts and they had not reached normal at the end of the period of observation.

Again, as in Case 5, the volume of bile did not parallel the secretion of bile acids and cholesterol. Since very little bile entered the intestinal tract during the first part of the postoperative period, the volume of bile obtained from the fistula represents a fairly accurate measure of the total bile volume. Furthermore, during this period there were no bile salts found in the urine and there was also a rise in the serum bili-

rubin which would indicate a very marked suppression of the activity of the liver cell.

Cholic acid first appeared in the specimen obtained during the 24 hours in which the administration of bile salts was started. The bile salt content rose rapidly to the level found in the control cases, but the cholesterol content of the bile did not increase to the same degree. It would appear that in this case the liver was unable to form cholic acid from the precursors present in the body, but that it was able to secrete this substance into the bile when it was supplied to the hepatic cell by the portal blood from an exogenous source.

The increase in the volume of the bile obtained from the fistula in Case 10 demonstrated that the bile salts are cholagogic as well as choleretic.

The increased elimination of bile salts was followed by a decrease in the serum bilirubin which was indicative of improvement of the pigment metabolism. Along with these changes there was a marked rise in the caloric intake and all of these changes were reflected in the clinical improvement observed at this time in the patient. The patient gained strength; his mental state improved; he was more alert and interested in his surroundings.

The maximum concentration of bile acid in this bile was obtained with a dose of 3 gm. of the bile salts per day. When this dose was increased to 4 gm., the stool specimens became positive for bile salts and a digestive upset occurred in the patient. However, this maximum output of bile acids did not equal the maximum concentration of bile acids observed in other cases in which there was no evidence of intrahepatic pathology. The degree of hepatic damage in this case is shown by the fact that the hippuric acid test, taken at the end of the period of study when the greatest amount of liver regeneration should have been present, revealed a detoxifying ability of only 50 per cent of normal. It is therefore probable that other hepatic mechanisms had not reached normal at this time.

SUMMARY AND CONCLUSIONS

1. In each case the composition of the human fistula bile was found to be remarkably constant in spite of a variable diet.

2. A marked increase in the concentration of the bile acids in this fistula bile was produced by the oral administration of bile salts. The increase in the bile acids was not accompanied by a proportionate increase in the cholesterol content of the bile. It was therefore possible by the oral use of bile salts to alter the bile salt-cholesterol ratio of the bile secreted by the liver.

3. The portion of the bile acids conjugated with taurine was not increased to the same level as the other bile acids present in this fistula bile.

4. Following surgery of the extrahepatic biliary system there was a short period of decreased bile acid secretion. This period of depressed activity was accentuated by hepatic damage.

5. The bile volume did not parallel the rate of excretion of bile acids and cholesterol.

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CASE REPORTS

Case 1. A. D., a white female, age 65, had had typical attacks of gall bladder colic over a period of 19 years accompanied by a definite intolerance for fat and fried foods. There was no history of jaundice during or following an attack. All laboratory studies were normal at the time of admission. Cholecystogram revealed a non-visualized gall bladder. The patient was operated on October 22, 1936, and a cholecystectomy and choledochostomy were performed. Several faceted gall stones were removed and the gall bladder showed evidence of chronic cholecystitis. No choledochal stones were found. The postoperative course was uneventful. No vomiting occurred after the first day and the patient was given the usual postoperative diet. The collection of bile from the catheter in the common bile duct was begun as soon as the patient returned from surgery and was continued until the tube was removed 10 days later.

Case 2. H. P., a white female, age 50, who had had several previous attacks of gall bladder colic, was admitted to the hospital because of jaundice which had occurred following an attack of pain. The onset of the present attack had begun suddenly 3 weeks prior to admission. Serum bilirubin was 5 mg. per cent at the time of admission. Three days later the patient was operated and a stone was removed from the common bile duct. A rubber catheter was placed in the duct. There was a moderate postoperative reaction following this surgery, but the patient's temperature was normal on the third day and there was no vomiting. The remainder of the postoperative course was entirely uneventful. The collection of bile was not begun until the eleventh day, and this was continued until the seventeenth day. During this time the patient was on the routine hospital diet. The patient did not receive any bile salts during period of hospitalization.

Case 3. M. W., a white female, age 59, was admitted to the hospital and operated as a case of ruptured appendix. The onset of the present attack occurred two days prior to admission with severe pain along the right infracostal margin with subscapular radiation. The pain had been present continuously since the onset and had increased in severity. There had been no nausea or vomiting. Although the patient had had intolerance for fat and fried foods, there had been no definite attacks of gall bladder colic.

The patient gave history of an arrested case of pulmonary tuberculosis and had had eleven pregnancies with one miscarriage. When the abdomen was opened, an acutely inflamed hemorrhagic gall bladder was found. One large gall stone was removed. The gall bladder was not removed and a simple cholecystostomy was done. The specimens of bile were collected from the drainage tube placed in the gall bladder. Biliary drainage was collected from the first to the eleventh postoperative day. The patient did not receive any bile salts during the preoperative or postoperative period.

Case 4. E. F., a white female, age 62, was admitted to the hospital during an acute attack of pain in the right upper quadrant, which had been present for five days accompanied by nausea and vomiting. The patient gave a history of similar attacks over a period of two years. There was no history of jaundice and there was no definite food intolerance. The patient had had typhoid fever twenty

years ago. She had had nine pregnancies. On admission the oral temperature was 101° F. and the white blood cell count was 17,000.

The patient was taken to surgery as an emergency. The appendix was found to be normal, but the gall bladder was acutely inflamed and gangrenous, with a stone wedged in the cystic duct. A cholecystostomy was done and the bile was collected from the tube placed in the gall bladder. The postoperative course was very stormy and the patient ran a high temperature with a marked degree of abdominal distention. Drainage from the tube in the gall bladder stopped on the seventh day, but there was profuse biliary drainage from the wound around the tube. The convalescence was long and she regained her strength slowly. No bile salts were given.

Case 5. F. G., a white female, age 52, was admitted during an attack of gall bladder colic. She complained of severe epigastric pain and at the time of admission a slight degree of icterus was visible (serum bilirubin 2.1 mg.). Cholecystogram revealed an opaque biliary calculus with nonvisualization of the gall bladder. Six weeks after admission, when the serum bilirubin had decreased to 1 mg., the patient was operated. Due to numerous dense adhesions the surgery was extremely difficult, and a stone could be removed from the common bile duct only by a transduodenal approach. A catheter was placed in the common duct. The postoperative period was very stormy. The patient died on the third day with a hyperpyrexia and rapid pulse. The death was a typical "liver death" due to combined hepatorenal failure. Specimens of bile were obtained from the catheter in the common duct at 24 hour intervals. No bile salts were given either preoperatively or postoperatively.

Case 6. G. S., a white female, age 38, had had pain in the upper right quadrant without subscapular radiation for 3 months prior to her admission. There was no history of food intolerance, previous attacks of gall bladder colic, or visible jaundice.

At the time of admission, a smooth, movable mass, which was very tender, had been palpated in the gall bladder area. The patient was seen by both the urological and gynecological services in consultation, and on July 29, 1936, an exploratory laparotomy was performed. The mass in the abdomen was found to be an enormously distended gall bladder with a stone impacted in the cystic duct. A choledochostomy was done along with the cholecystectomy.

No bile salts had been given preoperatively, but on the fourth postoperative day 'Bilron' (Iron Bile Salts, Lilly) was begun. Twenty-four hour specimens of bile were collected for a period of 14 days. The regular postoperative dietary regime was followed and recovery was uneventful.

Case 7. M. S., a white female, age 28, had been under observation at irregular intervals in the Out-Patient Department of the Indianapolis City Hospital since 1927. During this period she had had several attacks of gall bladder colic. The pain had shown definite subscapular radiation and there was residual tenderness over the gall bladder area after an attack of pain. However, the patient did not give a history of any visible jaundice or fever either during or after an attack. A marked degree of food intolerance and constipation had been present for several years prior to the first attack of pain. In view of this typical history and a positive cholecystogram, which was made in January, 1936, a diagnosis of cholelithiasis was made, but because the patient was only one month postpartum, she was given a trial period on a medical regime which consisted of a low cholesterol, low carbohydrate diet and the use of bile salts. The patient remained symptom free for 27 days, but at the end of this period had another attack of gall bladder colic. Since the patient was now two months postpartum, surgery was advised, and on March 21, 1936, she was admitted to the Indianapolis City Hospital.

Hippuric acid test for liver function was done at this time and 2.58 gm. of benzoic acid were recovered from the urine with a urea clearance of 85 per cent. The serum bilirubin was .8 mg. 100 c.c. and the blood cholesterol was 133 mg. 100 c.c.

Nine days later a cholecystostomy was performed and the gall bladder was found to contain several faceted gall stones and a large amount of dark concentrated bile, which was aspirated for analysis. Twenty-four hour specimens were collected from the drainage tube which had been placed in the gall bladder.

As soon as possible after surgery 'Bilron' was started. For the first two days 1 gm. was given daily and then the dose was increased to 2 gm. Vomiting did not occur after the first day. The entire postoperative course was uneventful, and the drainage tube was withdrawn on the tenth postoperative day.

Case 8. K. S., a white female, age 52, was admitted to the Indianapolis City Hospital on May 16, 1936, during an acute attack of upper right quadrant pain accompanied by chills, fever and jaundice. This attack had begun two weeks prior to admission as a sudden sharp pain in the epigastrium which had been followed by nausea and vomiting. The jaundice had become definitely visible, and at the time of admission the serum bilirubin was 10 mg. and was of the obstructive type.

This patient had had a long series of similar attacks of gall bladder colic prior to a cholecystectomy in 1930. After the cholecystectomy the patient had continued to have digestive symptoms, chiefly food intolerance and constipation, interspersed with an occasional attack of upper right quadrant pain. On one other occasion the patient had become jaundiced during an attack of pain.

Examination revealed an area of tenderness in the gall bladder region with some muscular rigidity. There were no other physical findings. A hippuric acid test with a four hour excretion of 2.21 gm. of benzoic acid (urea clearance 49 per cent) and a galactose tolerance of 2.17 gm. of galactose excreted in 4 hours, would indicate a fair degree of hepatic function. Furthermore, the serum bilirubin decreased rapidly from 10.7 mg. to 3 mg. per 100 c.c. and on June 1, 1936, an exploratory laparotomy was performed. A small common duct stone and amorphous debris were removed from the common bile duct and a rubber catheter was placed in this duct. Twenty-four hour specimens of bile were collected from this tube. The postoperative reaction in this patient was very severe and for several days the temperature was very high and vomiting occurred. However, by the fourth day the temperature had reached normal and the remainder of the postoperative course was uneventful. 'Bilron' was begun on the tenth day postoperatively and continued until the tube was removed from this duct on the thirteenth day.

Case 9. A. S., a white female, age 53, was admitted to the Indianapolis City Hospital on April 15, 1936, with a diagnosis of acute cholecystitis. The patient had had severe upper right quadrant pain for 3 weeks prior to her admission and there was definite tenderness present and a mass was palpable in the gall bladder area when the patient was first seen in the hospital. The pain in this instance was not accompanied by jaundice, but nausea and vomiting did occur frequently. Likewise, a history of intolerance for fat or fried foods with constipation was not given. In fact, the patient had never had any abdominal pain prior to onset of the present attack.

The patient was operated after the acute attack had subsided, and when the abdomen was opened, a bulbous gall bladder was not removed, but a rubber tube was placed in each tract and these tubes were connected by means of a Y tube with a container. Twenty-four hour specimens of bile were collected for analysis. The convalescence was entirely uneventful. 'Bilron' was begun on the fifth day postoperatively and 1 gm. was given daily until the tubes were removed from the gall bladder.

Case 10. O. T., a white male, age 56, was admitted to the Indianapolis City Hospital on August 1, 1936, because of a painless jaundice which had been present for 3 weeks. With the exception of a mild degree of nausea and vomiting and itching, the patient had had no other symptoms since the appearance of the jaundice. The patient had been aware of a loss of strength during the past several years, but there was no definite loss of weight. The patient had never had an attack of gall bladder colic, nor had he shown any symptoms of a cholecystitis. In March of 1936 the patient had had a basal cell carcinoma removed from the right cheek in the preauricular area. This was a typical rodent ulcer. This wound had healed and there was no evidence of extension at time of present illness.

After admission there was no elevation either of temperature or the white blood count. The jaundice continued to increase until the serum bilirubin reached 10.9 mg. per 100 c.c., but after large amounts of intravenous glucose, the serum bilirubin gradually declined until in 3 weeks it had reached 3.5 mg. At this time an exploratory laparotomy was performed, because it was believed that there was an obstruction of the common bile duct due to some malignant growth in the head of the pancreas. However, on exploration, there was no obstruction found in any of the extrahepatic biliary system, although a small discrete tumor was found in the head of the pancreas. This tumor was not believed to be malignant and was so located that it could not have caused an obstruction of the common duct. The gall bladder was removed, but no stones were found, and the cholecystitis was of a mild chronic nature. The liver appeared swollen and edematous and somewhat darker than usual. The cause of the jaundice was not believed to be an obstruction of the intrahepatic biliary ducts. A rubber T tube was placed in the common duct and the collection of bile was begun.

The immediate postoperative course was very stormy. The patient had a high temperature for several days, was given one blood transfusion and several injections intravenously of 10 per cent glucose solution. By the eighth day his condition had improved sufficiently so that he was able to take some food and was not vomiting. The serum bilirubin had increased after surgery until on the eighth day it was 4.7 mg. The differential analysis of the fistula bile was begun on the eighth day and continued for the next 20 days. The administration of 2 gm. of 'Bilron' was started on the eleventh day. There was no vomiting or other untoward symptoms and the patient showed a marked clinical improvement after the bile salts were started. He gained strength; his appetite improved; and, in general, he seemed brighter and more alert mentally. The dose of 'Bilron' was gradually increased until the patient was receiving 4 gm. daily.

The exact intake of food was recorded during the period of observation. Frequent determinations of the serum bilirubin, urinary urobilinogen, urobilin in stools, and bile salts in the stools were made.

On the 39th postoperative day the T tube was closed, and, since no jaundice developed after a period of 2 weeks, the tube was removed. The fistula closed rapidly and the patient was released from the hospital on the 60th postoperative day.

Just before the patient was released from the hospital a hippuric acid test for liver function was determined and the output of benzoic acid in 4 hours was 1.88 gm. with a urea clearance of 88 per cent. This would indicate that, although all evidence of jaundice had disappeared, there was still a marked impairment of the hepatic function.

Gastroscopy as a Diagnostic Procedure*

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SINCE the introduction of the Wolf-Schindler flexible gastroscope four years ago, gastroscopy has become a well recognized diagnostic procedure. For many years prior to the development of the flexible instrument, a number of different types of rigid gastroscopes had been tried, and discarded on the basis that the information thus obtained was not of sufficient value to justify the risk incurred. With the advent of the flexible gastroscope, the danger of the procedure was practically overcome, and the diagnostic importance of this type of gastroscopic examination was fully established. The flexible gastroscope is a closed instrument and can be used only for diagnostic study, but with it, almost the entire surface of the stomach may be brought into view. This is not possible with the rigid open tube instrument.

THE RIGID GASTROSCOPE

The rigid open gastroscope however, still has a definite place in the diagnostic study of lesions in the cardiac end of the stomach, and in the management of foreign bodies lodged in the stomach. When the lesion infringes upon the cardia, not only may the lesion be brought into view with the open tube gastroscope, but this type of instrument provides the only means by which a specimen may be removed for microscopic study, thus enabling one many times to make a correct diagnosis. We have had seven cases of carcinoma of the cardiac end of the stomach in which the diagnosis had not been made by routine studies, but was easily made with the open tube gastroscope. The rigid open tube gastroscope is of the utmost value in the management of foreign bodies in the stomach. In most instances in which the foreign body will not pass through the pylorus, it can be removed through the open tube gastroscope, providing of course, the instrument is in the hands of one properly trained for such work, and the necessary X-ray equipment is available. Under no other circumstances should the gastroscopic removal of a foreign body from the stomach be attempted—the risk is too great, and the attempt will usually meet with utter failure.

THE FLEXIBLE GASTROSCOPE

The introduction of the flexible gastroscope is accomplished without much difficulty. However, great care should be observed in introducing the instrument into the esophagus, especially when it passes the cricoid level. This is the narrowest portion of the esopha-

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gus, and is the location where trauma and perforation are most likely to occur. When the instrument passes this level, no further difficulty is likely to be encountered except a momentary delay at the cardia. With the instrument in the stomach, the most important landmark is the angulus. This comes into the field of vision as a fold coming off from the lesser curvature. Sometimes, as Schindler has stated, it has the appearance of a twisted cord which stands out in a very characteristic manner. With the angulus located, a slight increase in the depth of the instrument should, and usually will, bring the antrum into full view. The pylorus is readily seen in the majority of cases *through*, or as one might say, *at the depth* of the antrum. With the patient in the gastroscopic position, the mucous lake, which is nothing more than a collection of mucus and other gastric secretions in the most dependent portion of the stomach, is another landmark which is helpful in some cases in localizing the portion of the stomach that is under observation, but it is of very minor importance as compared with the angulus.

After some experience in gastroscopic examinations, the appearance of the area under observation is sufficient to give one a very definite idea as to the portion of the stomach being studied. The mucous membrane along the lesser curvature is always quite smooth, and never shows any folds. This smooth appearance of the mucosa is not noted in any other portion of the stomach. Both the anterior and posterior walls are thrown into folds, the general direction of which is towards the pylorus. The folds on the anterior wall are quite shallow and run parallel to the longitudinal diameter of the stomach, converging into the antrum. The folds on the posterior wall and on the greater curvature are quite deep and broad when compared with those on the anterior wall; they too, converge towards the antrum, and fade out somewhat and become less marked as the antrum is approached.

The gastric image is influenced by the change in the position of the stomach due to respiratory movements, by the position of the patient on the examining table, and by the peristaltic activity of the stomach itself. The change in the position of the stomach due to respiratory movements may interfere somewhat with the gastroscopic image, but we do not believe that this change is sufficient to be of any great moment in preventing one from obtaining a clear visual field. A faulty position of the patient on the examining table materially interferes with clear vision. This may either be due to a faulty position of the head, a faulty position of the body, or both. Otherwise expressed, if the patient is not in the proper position on the examining table, a clear visual field cannot be obtained. We have frequently noticed that when an examination is prolonged and the patient becomes somewhat tired, distortion of the visual field may occur, due to the patient assuming a faulty position. It is therefore, quite important not to continue the examination longer than absolutely necessary to actually make a careful study of the stomach wall. This usually requires only a very few minutes.

PERISTALSIS

Peristaltic activity of the stomach is constantly changing the appearance of the visual field, especially in the antral and pre-antral zones. When the antrum is free from peristaltic activity, it is seen as an oval or almost round opening three-quarters of an inch or more in its longest diameter, in the depth of which the pylorus is readily seen. When a peristaltic wave passes over the pre-antral area and approaches the antrum, the entrance to the antrum appears as a mere slit. As the wave passes over the antrum toward the pylorus, the entrance to the antrum is again clearly seen. When the wave actually passes over the pylorus, the pylorus will be seen to close, and the mucosa of the antrum will be thrown into rather symmetrical folds, which gives the pylorus a drawn-in puckered appearance. After the peristaltic wave has passed over the pylorus, and before the next wave appears, one is usually able to obtain a clear view of both the antrum and pylorus. During this period of motor activity of the stomach, that is, between the peristaltic waves, and when the antrum is open, the pylorus may be seen rhythmically opening and closing. While we cannot be sure as to the exact time when one sees the open pylorus to the best advantage, our impression is that it occurs shortly before the peristaltic wave coming down over the pre-antral zone reaches the antrum. This is probably due to the fact that when the peristaltic wave passes over the antrum, the latter for a short period of time is completely closed off from the body of the stomach. If watched carefully, the peristaltic wave can be seen first to close off the antrum completely, but as it passes downward, the antrum will be seen to open, and shortly afterward, the pylorus will be seen to close. The further one withdraws the gastroscope away from the pylorus, the less the gastroscopic image will be disturbed by peristaltic activity. In the body and cardiac end of the stomach, peristaltic activity is a negligible factor in changing the gastroscopic image. The peristaltic activity that we have endeavored to describe, is that which we believe occurs in the normal stomach. In the beginning of our gastroscopic studies with the flexible gastroscope, we selected cases in which regular routine gastrointestinal studies, including a carefully taken history, physical examination, chemical analysis, stool studies for occult blood, and complete gastrointestinal X-ray studies, failed to reveal an organic lesion in the gastrointestinal tract.

We believe that all beginners should study a large number of normal stomachs before beginning to study cases which are known or suspected of having definite pathology. Without being perfectly familiar with the appearance of the normal mucosa, one cannot appreciate or detect pathological changes when present. In some of our normal cases, we made as many as a dozen gastroscopic examinations. We made at least fifty normal gastroscopic examinations before we undertook to study cases in which a lesion of the stomach was even suspected.

We have always used the same technique. For lighting purposes, we use a battery with a volt meter, so as to have a constant amount of current at all times; otherwise, one would be likely to have enough variation in the strength of the current to produce a change in the brightness of the light, which would naturally change the appearance of the gastroscopic image. Any change in the brightness of the light would make it very difficult to read one's findings with an equal degree of accuracy.

VALUE OF GASTROSCOPY

While a gastroscopic examination is very helpful in the diagnosis of any lesion of the stomach, its greatest value is in that group of cases in which our present

routine examinations are of the least value, namely—the different types of chronic gastritis and obscure gastric hemorrhage. In the study of suspected cases of carcinoma of the stomach, we believe that early routine gastroscopy may reveal the lesion before it is possible to make a diagnosis by our usual diagnostic procedures. In our gastroscopic studies so far made, we have met with two most unusual cases. In one, an X-ray diagnosis of carcinoma of the body of the stomach had been made, but a gastroscopic examination failed to show any evidence of malignancy. This was one of our early cases, and we thought that our inability to find the lesion was due to lack of experience. This patient was operated upon and no evidence of malignancy was found. In the other, an X-ray diagnosis of malignancy of the stomach involving the prepyloric region had been made, while the gastroscopic examination showed the malignancy to be very much more extensive—cancerous nodules were found scattered throughout the body of the stomach to within a short distance of the cardia. This patient was also operated upon and nearly all of the stomach was found to be involved in the cancerous process. These two cases suggest at least, that gastroscopy is of value not only in helping to determine the presence of carcinoma, but also in determining the extent to which the stomach is involved, and whether or not anything is likely to be gained by operative treatment.

From our experience with gastroscopy, we are convinced that both X-ray studies and gastroscopic examinations should be made in all cases of suspected malignancy of the stomach. While gastroscopy with the flexible gastroscope is a comparatively new diagnostic procedure, we are quite convinced that in the diagnosis of early malignancy it will be found to be of the utmost importance. Likewise in the differential diagnosis between carcinoma and ulcer, it will be found to be of great value. In not a few cases, the decision as to whether or not the lesion under consideration is malignant or benign, will be decided by the gastroscopic examination. This statement may seem to be a little bold, but never-the-less, we believe it will prove to be true.

In the study of advanced malignancy, the diagnostic value of gastroscopy is of very much less importance. In the advanced cases, the diagnosis can readily be made by the present routine methods of examination. As previously stated, its greatest value is not in the study of malignant disease (except in the early cases where malignancy is only suspected or in the study of gastric ulcer), but in the study of the different types of chronic gastritis, and in the study of obscure gastro-intestinal hemorrhage.

CHRONIC GASTRITIS

Some of our leading gastro-enterologists believe that chronic gastritis in some form is a very definite predisposing factor in the development of carcinoma, in that carcinoma does not develop in a normal stomach, but in one already diseased. They also further believe that chronic atrophic gastritis is the one disease that is prone to be followed by gastric carcinoma. Therefore, if this etiological relationship of chronic atrophic gastritis to carcinoma of the stomach is proved to be true, it at once places this type of gastritis in the front rank, among the organic lesions of the stomach. For many years, with few exceptions, very little thought or consideration was given to the study of chronic gastritis. With the development of gastroscopy, especially with the flexible gastroscope, the condition is now known to be of quite frequent occurrence. It would therefore seem from recent gastroscopic studies, that it is probably the most frequent of gastric diseases.

Schindler classifies chronic gastritis as follows: superficial gastritis, atrophic gastritis, hypertrophic gastritis, and gastritis following operations upon the stomach. For clinical purposes, we are convinced that this classification is entirely satisfactory. The cases readily fall into these groups, and are quite easily recognized gastroscopically. In our gastroscopic studies, we have seen all grades of inflammatory changes in the mucosa, varying from the very mild grades of superficial gastritis to the very severe grades of hypertrophic gastritis. We have studied the changes in the gastric mucous membrane that occur associated with duodenal ulcer, and also those that follow operations upon the stomach.

SUPERFICIAL CHRONIC GASTRITIS

In the very mild cases of superficial chronic gastritis, the mucous membrane is somewhat redder than normal, and frequently has a slightly granular appearance. Superficial abrasions and hemorrhage into the mucosa occur rather frequently. These changes occur mostly in the antrum and pre-antral zones. It is not infrequent also, to find varying quantities of thick tenacious mucus adhering to the antral folds, or scattered throughout the pre-antral zone. We have also found small hemorrhagic areas with practically no other changes in the mucosa, in cases that did not have digestive symptoms, and where we did not expect to find any evidence of gastric disease. Just what the significance of these hemorrhagic areas is, we are not in a position at this time to state. By further observation, we hope to determine their significance, if any. Whether they have any relation to the development of peptic ulcer later on, is a question for someone to solve. The findings just described, while found mostly in the antral and pre-antral zones, may extend to a less degree upward over the body of the stomach. In this type of chronic gastritis, there is very little distortion of the mucosal folds, and practically no edema. It seems logical to state that in this form of the disease, with an appropriate diet and proper medical treatment, the symptoms should disappear and the stomach function return to normal.

CHRONIC ATROPHIC GASTRITIS

This form of chronic gastritis is characterized by atrophy of the mucosa. The mucosa loses its orange or orange red color, and assumes a grayish hue, described by Schindler as gray-green in appearance. This color change is easily recognized gastroscopically. While there is some alteration in color throughout the entire gastric mucosa, the real characteristic changes occur in localized areas, chiefly in the pre-antral zone. In these atrophied areas, one frequently sees the blood vessels very distinctly, which finding is quite characteristic of chronic atrophic gastritis. In the normal stomach, the blood vessels are seldom visible gastroscopically. The atrophic areas vary in size up to two centimeters or more in diameter. The mucosal folds are less marked on both the anterior and posterior walls, giving the stomach a somewhat smoothed-out appearance. Frequently one also sees superficial ab-

rasions and hemorrhagic areas associated with these changes. Some observers believe that superficial chronic gastritis is followed quite frequently by the atrophic form. There can be no question that some of the changes in the mucosa that are found in chronic superficial gastritis, are also found in the atrophic type of the disease. No case of complete atrophy has so far come under our observation.

CHRONIC HYPERTROPHIC GASTRITIS

In this type of gastritis, the mucosa presents an entirely different picture. The mucous membrane is very red and angry looking, abrasions and hemorrhagic areas are more frequently seen than in the atrophic form, and the amount of thick tenacious mucus is increased. The entire mucosa may be involved. These changes appear to be more marked in some areas than others, and are especially prone to occur in the pre-antral zone. The mucosal folds are swollen and broader in appearance; in some places, they seem to adhere to each other. Quite frequently the folds appear edematous and so swollen, that they are nodular in appearance. Large hemorrhagic areas are frequently noted. The whole picture is so characteristic, that one has very little difficulty in recognizing the condition.

GASTRIC HEMORRHAGE

Gastric hemorrhage is a definite indication for gastroscopy, when the usual routine examinations fail to reveal the source of the bleeding. One very important precaution however, should be taken—one must rule out a lesion of the esophagus as the cause of the bleeding. This can only be done by an esophagoscopic examination, which should always precede gastroscopy in this group of cases. Many times esophagoscopy will reveal that the bleeding is coming from the esophagus, frequently due to varicose veins. Such a finding of course, is a definite contraindication for gastroscopy. If nothing is found in the esophagus to account for the bleeding, gastroscopy may, and frequently will, locate the source of the hemorrhage.

DUODENAL ULCER

The small number of gastroscopic studies made in duodenal ulcer to date, do not permit us to draw accurate conclusions. The findings so far, however, seem to indicate that in those cases of duodenal ulcer in which the emptying time of the stomach is more or less definitely delayed, one will usually find superficial chronic gastritis in the antral and pre-antral zones. Further observations in this group of cases will be made and the results of the studies reported later.

GASTRITIS FOLLOWING OPERATIONS UPON THE STOMACH

The studies in this group have been limited to cases that had had a gastro-enterostomy performed for peptic ulcer, but had not been entirely relieved of their digestive symptoms following the operation. In all of the cases examined so far, we found a very active gastritis surrounding the stoma, spreading for some distance from the stoma and gradually fading out into normal mucosa. In a few instances, the gastritis was more extensive and involved almost the entire stomach. In not a single case did we find any evidence of marginal ulceration. Marked improvement in the gastritis occurred following the use of a bland, non-irritating diet without any other treatment. A few cases in which the digestive symptoms had been relieved following gastro-enterostomy were also studied. In this group, no evidence of gastritis was found. The entire mucosa was perfectly normal in appearance.

The Galactose Tolerance and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice*

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WE do not propose to go far into the large and confusing field of liver function tests, but simply to describe our results with these two well-known tests in eighty consecutive cases of jaundice in the medical wards, mostly over the age of 35, to see how much or how little they have helped in diagnosis.

By "painless jaundice" we mean cases without pain or in which pain was a mild or minor symptom. The group consists of 17 cases of acute infectious hepatitis (catarrhal jaundice), 17 cases of acute toxic hepatitis, 12 cases of obstruction of the common bile duct, and 34 chronic intrahepatic cases, mostly cirrhosis, with an acute exacerbation of jaundice. We have chosen this group of liver cases for study since here the most common mistakes are made in distinguishing "medical" from "surgical" jaundice. The mistakes are serious because prompt surgery for obstructive jaundice is the rule, while operation is needless and often dangerous when there is no obstruction outside the liver.

Liver function tests are confusing, there are so many; also disappointing because of the very large margin of safety in the liver, and the effects of regeneration of tissue. Liver function tests may be used in several ways, depending on the kind of information we want to get. First, we may try to detect the presence and amount of liver damage, second, we may use them for differential diagnosis of liver disease; third, we may follow the progress of the disease in the liver; fourth, we may use them for prognosis.

For the first purpose, the *icteric index* and *bromsulphthalein* or *rose bengal* tests are among the best, but since they are positive in practically every case of jaundice, they have little differential value. For the

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second purpose, the *urobilinogen* and *galactose* tests were chosen. Although we did not expect them to prove adequate routine tests of liver function, we hoped they would react differently to different types of jaundice. The tests have also the advantage of being simple and easy.

THE TESTS

These tests are so well known that they need little description. In the *Bauer galactose test* 40 grams of galactose dissolved in 500 c.c. of water and flavored with a little lemon juice is given fasting in the morning. All the urine passed in the next five hours is collected, and the amount of sugar determined. 75% of the figure found by Benedict's Solution (for glucose) equals the amount of galactose. Over three grams is considered a positive test. One function of the liver is the conversion of galactose into glycogen. The kidney has practically no threshold for galactose and if any is circulating in the blood some is excreted in the urine. The urine has been tested for galactose rather than the blood, since the latter test is far more elaborate and complex without any corresponding advantage. Galactose appears to be the best sugar for this metabolism test. It is easily absorbed, causes no gastro-intestinal disturbance, the normal tolerance is well known, and the dose is fairly independent of the size, age, or sex of the patient.

For the *urobilinogen test* we add 1 c.c. of Ehrlich's reagent (2 gr. paradimethylamidobenzaldehyde in 100 c.c. of 20% HCl) to 10 c.c. of fresh urine. If positive, a cherry red color appears in three or four minutes. The test can be made quantitative, according to Wallace and Diamond, by diluting the urine 1-10, 1-20, 1-40, 1-80, etc., until the urine just fails to show a faint red color looking through the tube from top to bottom. No antipyrine, hexamethylamine, or pyridine should be given during the test, as they may give false urobilinogen reactions with Ehrlich's reagent. If the test is positive in over one to twenty dilutions, it is considered abnormal. We have run 200 normal controls during this series of tests. To avoid variation in individual specimens of urine, a quantitative test of urobilin in the 24-hour urine could be used, but at present it is rather elaborate, and very exact methods seemed needless, as we were only concerned with gross changes.

The theory of the test is simple. There is little doubt at present that urobilinogen (and urobilin) are formed within the bowel by bacterial action whenever bile pigment is present in the bowel. Part of it is excreted in the feces and the rest is carried to the liver by the portal system. If the liver is normal, it is properly mobilized and possibly used again in the formation of new hemoglobin, and very little or none is eliminated from the blood by the kidney. A damaged liver is unable to normally convert the urobilinogen and its increased output in the urine is a sign of liver dysfunction. As far as we know there is little or no renal threshold for urobilinogen and the amount which appears in the urine is roughly proportional to the amount of damage to the liver function, but in hemolytic disease there may be a great increase in the formation of bile pigment, and thus the amount of urobilinogen in the bowel and urine is increased without indicating liver insufficiency.

We recognize the variability of both tests and other theoretical objections. Galactose in normal persons passes easily through the kidney but there may be a renal threshold in nephritis which limits its excretion. In addition to the liver a group of other organs such as the pancreas, thyroid, ovary and pituitary body are concerned in the metabolism of galactose.

Urobilinogen varies considerably in amount in different specimens of urine from the same patient, and is slowly converted to urobilin on standing so that fresh samples of urine are needed. The loss in urobilinogen is about 20% in 24 hours if the urine is placed in a cool, dark place, but in a warm, light room nearly all the urobilinogen is converted into urobilin in twenty-four hours.

We do not believe that these objections are important in this group of cases for two reasons: first, because only gross changes have value in differential diagnosis, for example: the constant absence of urobilinogen in one case compared with its constant increase in another; second, on account of the type of cases examined. We were not dealing with hemolytic jaundice in which our present diagnosis is about 100% accurate, and which strongly affects the amount of urobilinogen in the urine. We were not dealing with marked nephritis which would interfere with the excretion of sugar or pigments. We were not dealing with definite endocrine disturbances such as thyroid, pituitary, or adrenal disease which would influence the sugar metabolism. No diabetics were met in this series.

We soon learned the variation in urobilinogen which occurs from day to day, from morning to afternoon, and at different stages in an attack of jaundice, and learned *the necessity for a course of six or eight urobilinogen tests*, beginning early in the attack, if possible, or at the height of the jaundice and extending over ten days to two weeks, which is very easy to do since the test is so simple. A course of tests is usually far more valuable than any single test which has limited value and may even be misleading. In a doubtful case of obstruction of the common duct we can usually well afford to wait a week or two and run a series of tests to try to rule out intrahepatic jaundice.

On account of the dissociation of functions in the liver, it seemed logical to use two kinds of tests in addition to the icteric index in order that one test might back up the other. For example: the urobilinogen test is quite constantly positive in all kinds of liver disease *except* where no bile reaches the bowel. The galactose test, on the other hand, is less sensitive, but is independent of the presence of bile in the bowel. While the tests do not accurately measure liver function they may be used to differentiate one pathologic process in the liver from another.

RESULTS

The cases are grouped as acute infectious, and toxic hepatitis; obstructive jaundice, and chronic intrahepatic jaundice, mostly cirrhosis. The basis for the classification of cases has been the clinical history and examination, with special effort to discover a possible cholecystitis in the cases classed as infectious hepatitis; by operation or autopsy in the cases of obstructive jaundice; and by the clinical course in the cases of chronic intra-hepatic jaundice, supplemented by some biopsies and autopsies. The tables show the age of the patient, the duration of the jaundice, the maximum jaundice as measured by the icteric index, the galactose excretion in grams, and the urobilinogen in urine. The latter figures represent the greatest degree of dilution which gave a positive test, e.g. 40 means present in 1-40 dilution, etc.

Infectious Hepatitis (Catarrhal Jaundice). In seventeen cases, fourteen gave a positive urobilinogen test at some period of the disease and ten cases a positive galactose test. In looking over the group it was found that of the seven negative galactose cases, three were

very mild cases (Cases 1, 2 and 3) and in one (Case 4) the tests were first made in the late convalescent stage of the jaundice. So, it seems desirable to divide these cases into two groups. A mild or convalescent group with the duration of the jaundice only two or three days and with an icteric index of 10-40, and a well-marked group with the duration of the jaundice from one week to one month and an icteric index of 25 to 250.

In the five cases of the mild or convalescent group the galactose test was normal in all and the urobilinogen was positive in four. In this mild group the tests were not particularly needed for diagnosis and the galactose test gave no help. In several of these mild cases (Nos. 1, 3, 4 and 5) where the carbohydrate function showed no change and the galactose test was within normal limits, the positive urobilinogen test had definite value in indicating the true nature of the

GROUP I

TABLE I

Acute infectious hepatitis (Catarrhal Jaundice)

Case	Age	Weeks of Jaundice	Icteric Index	Galact.	Urob.	Remarks
			Mild or Convalescent			
1	15	½	25	0.61	80	convalescent
2	23	½	22	0.0	10	after vaccine
3	42	½	40	0.0	40	after vaccine
4	40	3	100	1.2	20	convalescent
5	45	1½	250	0.0	40	convalescent
			Moderate or Severe			
6	63	1	25	3.4	40	
7	40	4	140	4.6	20	
8	60	1	75	4.5	40	
9	55	1	100	7.4, 3.2	60	
10	22	2½	100	3.15	20	
11	53	3	100	5.5	80	
12	25	1½	100	5.2	32	
13	60	4	200	6.0	0	exc. 2.2L
14	25	5	145	4.5	80	
15	41	2	90	6.4	40	
16	28	2	90	4.1	40	
17	26	1	120	5.0	160	

Acute Toxic Hepatitis

Case	Age	Weeks of Jaundice	Icteric Index	Galact.	Urob.	Ketos	
1	35	1	75	4.0	40	+	empyema
2	28	1	150	5.6	80	++	acute hepatitis
3	45	2	100	5.4	40	—	pneumonia
4	40	1½	60	5.4	40	—	empyema
5	40	4	125	3.1	40	+	empyema
6	45	3	125	2.5	40	+	empyema
7	34	3	125	4.2, 5.0	80	+	empyema
8	41	4	70	3.0	20	+	empyema
9	37	1	60	3.0	320	—	empyema
10	32	1½	200	3.0	40	—	pneumonia, [illegible]
11	45	2	225	4.2	20	+	empyema
12	27	2	110	4.4	60	+	empyema
13	35	2	175	6.6	80	—	empyema
14	28	1½	250	3.6	80	—	empyema
15	30	1½	125	7.0	40	—	empyema
16	33	2	225	6.0	80	—	empyema
17	32	4	150	4.7	40	+	empyema

disease. In the remaining well-marked group of 12 cases the galactose test was positive in ten and the urobilinogen positive in ten. In two cases (Nos. 10 and 13) both tests were normal; they will be discussed below.

The course of the tests was interesting, showing the variation early and late in the jaundice, with different degrees of liver damage and recovery. When we had an opportunity to follow a well-marked case of infectious hepatitis from the start, the urobilinogen at first was moderately increased, then followed a period of a few days to a week when little or no bile reached the bowel, and we had the typical "clay stools," and the urobilinogen was negative. If the middle-aged patient is first examined at this period, the suspicion is raised of obstructive jaundice caused by cancer, a silent gall stone, or stricture of the common duct (more than half our infectious cases were between 40 and 60 years of age). It is here that the galactose test occasionally proved useful. It was usually positive at this time, indicating acute diffuse liver cell damage, and this was backed up by the clinical course, the return of bile to the stools, the high urobilinogen later, and the gradual disappearance of the jaundice.

In none of the 34 cases of infectious and toxic jaundice were the urobilinogen tests negative for more than one or two weeks (and usually only for a few days) at the period when no bile reached the bowel, and about three-quarters of the toxic and infectious cases reached the hospital when the "clay stool" period was passing or had passed and our urobilinogen tests were high from the start. In one case, a hospital officer, aged 28, with vague digestive symptoms for two weeks, nothing important was found on the first examination except a strongly positive urobilinogen test (in 1 60 dilution), which precede the appearance of jaundice by several days, and suggested the early diagnosis.

When we consider the four cases which did not follow the general rule, it is evident that the time of the test in relation to the period of the disease is very important. In Cases 4 and 5, the galactose tests were done only in the convalescent period and were both normal. In Case 10, the galactose test was first done and found normal just as the patient was beginning to rapidly recover; the icteric index dropped from 150 to 50 in the following week. This is also one of the rare cases where the urobilinogen remained within normal limits (the readings were: 8-16-0-2) in spite of intense acute jaundice.

In Case 13 we had real difficulty in diagnosis and the two tests gave no help. This was a sixty-year old man with two weeks of steadily increasing, deep, painless jaundice; the icteric index increased from 100 to 200. He had normal galactose tests and five urobilinogen tests showing complete absence over ten days; the diagnosis wavered between a sub-acute diffuse hepatitis with a long period of acholic stools and an obstruction of the common duct, and the patient was finally sent to the surgeon. A longer period of observation and tests might have avoided this mistake. The patient died of broncho-pneumonia a week later. At autopsy there was no obstruction of the bile passages but a late stage of moderate focal hepatitis with some regeneration of lobular cells. The bile capillaries were somewhat dilated. There was no cholangitis. The diagnosis was healing infectious hepatitis.

It is interesting to note that in the differential diagnosis between acute infectious hepatitis and obstructive jaundice the error has been only in one direction. One case of acute infectious hepatitis was wrongly called obstructive jaundice, no case of obstructive jaundice has been called infectious hepatitis.

The tests have definite value in prognosis. In the convalescence from acute infectious and toxic hepatitis the simple urobilinogen test has been especially useful in measuring the speed and degree of recovery of normal liver function. The milder cases clear up promptly, the more severe type with possible development of subacute yellow atrophy or cirrhosis show high residual urobilinogen tests long after the immediate symptoms have subsided.

Toxic Hepatitis. Of the seventeen cases, fourteen followed the use of arsphenamin, two of cincophen, and one of gold thiosulphate. All were well marked with jaundice lasting one week to one month, and a maximum icteric index of 45 to 160. In all cases the urobilinogen was increased, and was present in dilutions of 1/40-1/130. In all but two cases the galactose test was positive. In general the two tests were closely alike in the infectious and toxic groups, as might be expected. They were less important in diagnosis in toxic hepatitis when the history of the drug was obtained. See Illustrative Cases, No. 3.

The two cases of hepatitis in which the galactose test was not definitely positive followed arsphenamin. One (No. 4) was "suspicious" with 2.4 grams of galactose in the urine after the test and with urobilinogen of 40, and one (No. 9) showed no galactose in the urine after two tests, while the urobilinogen was present in 1/130 dilution. In these two cases with normal galactose tolerance, the strong urobilinogen tests were an aid in diagnosis of the condition of the liver.

Obstructive Jaundice. In our twelve cases are ten of cancer of the head of the pancreas, or common duct, and two benign cases, namely one large impacted stone in the common duct and one tight stricture of the common duct, the diagnosis was confirmed by operation in eight cases and post mortem in three. The ages were 43-69, the duration of the jaundice ten days to four months, and the maximum icteric index per case was 65-200. The stools in nine of the cases were gray or clay colored throughout, in two, light yellow at first and clay colored later. In the stone case they were variable. The liver was enlarged in nearly all of the cases, and the gall bladder was palpable in three. The spleen was not palpable in any case.

In the eleven cases of cancer and stricture, urobilinogen was almost entirely absent as a result of very little or no bile reaching the bowel. Four to eight tests were made in each of the eleven cases over a period of about two weeks with 69 negative and only one slightly positive test. The *absence* of urobilinogen in every case but one of marked obstructive jaundice (and the almost complete absence in every test) was a strong contrast to its *presence* in every case but one of infectious and toxic hepatitis at some time in the course of the jaundice, almost invariably in much increased amounts. The continued absence of urobilinogen was a valuable sign of marked obstruction of the common bile duct and since we have no really good test for bile in the feces, the urobilinogen test in the urine takes its place up to a certain point and is cer-

talnly much more definite than the often vague descriptions of the color of the feces. In our one case of silent stone in the common duct the galactose test was normal and the urobilinogen variable but always increased (40-80). It stands out in sharp contrast to the persistently negative tests in the other cases of obstruction.

In the "painless jaundice" group cancer involving test and a cholecystenterostomy was done. An autopsy showed a small cancerous stricture of the common duct 3 cm. above the papilla. The liver weighed 1570 grams. There was marked dilation of the hepatic duct. Microscopic examination showed stasis in the bile capillaries and a very moderate degree of damage of the lobular cells. She was one of our most severe and long-standing cases of jaundice, and the low galactose tolerance

GROUP II

TABLE II

Obstructive jaundice

Case	Age	Weeks of Jaundice	Urine Index	Galact.	Fistula	Diagnosis	P.M.
1	55	5½	300	6.51	0	Ca. pancreas	P.M.
2	48	7	125	4.92	0	Ca. pancreas	—
3	46	6	50	2.25	0 (stone)	Ca. pancreas	
4	70	3	75	4.83	0 (stone)	Ca. pancreas	—
5	74	3	45	3.52	0 (choledochotomy)*	Ca. pancreas	—
6	49	4	150	6.25	0	Ca. pancreas	—
7	75	12	200	4.5	0 (stone)	Stricture C.D. (Ca.)	P.M.
8	70	4	150	5.52	0	Ca. C.D. (Ca.)	P.M.
9	67	6	150	6.2	0	Ca. pancreas	—
10	63	10	50	5.2	0+0	stone C.D. (Ca.)	—
11	66	9½	60	6.6	0	Ca. pancreas	—
12	69	10	100	4.27	0 (all stones)	Ca. pancreas	—

*In Case 5, five urobilinogen tests were negative. One to 1 gave a faint positive test to undiluted urine.

the common duct predominates (ten of the twelve cases) and has produced an obstruction of a very complete type. Persistent acholia of the stools appears to be the rule in malignant obstruction of the common duct, and rarely occurs in other forms of jaundice. It often appears in hepatic degeneration but rarely lasts more than a week or so, often only a few days. The obstruction due to stone is rarely complete (see Case 10). This is clearly shown by these simple tests for urobilinogen and corresponds with the results obtained by C. J. Watson using a much more complete quantitative method of analysis of the 24-hour urine and feces.

A green color in the urobilinogen tests was found in four of the ten cases of cancerous obstruction and never in any other kind of case and it seemed possible that it might have special diagnostic value, but the literature shows otherwise. Simici and Popescu thought it was due to a precursor of urobilinogen. Umber and Bansi found it in severe toxic jaundice with transition into an acute yellow atrophy, and Jendrassik and Swartz finally showed that it has nothing to do with urobilinogen and has no relation to the severity of liver damage, but is due simply to the simultaneous presence of bilirubin and nitrites in the urine in sufficient concentration.

The galactose tests were normal in ten cases, suspicious in one (2.25 grams) and moderately positive in one (3.52 grams). The exceptional case was examined carefully for some explanation. She was a woman of 66 with cancer of the common bile duct. She had jaundice of over two months duration, gray stools with a complete absence of urobilinogen on six tests and a positive galactose test (3.52 grams). She was diagnosed as obstructive jaundice due to cancer, or common duct stone, regardless of the positive galactose may perhaps be due to more marked functional damage to the liver cells than was present in the other cases (even in the absence of marked histologic changes in these cells).

Chronic Hepatitis. Another group of middle aged patients, who may have an essentially painless jaundice, needs to be separated from the external obstructive or surgical group if possible. The tests were also used in this group to see if they would give additional diagnostic help.

The group of 34 patients included 23 cases of alcoholic portal cirrhosis, 1 hemachromatosis, 1 chronic toxic cirrhosis (CCl_4), 2 biliary cirrhosis (infectious), 1 Banti's disease, 1 syphilis of the liver and 5 chronic hepatitis associated with a pathological gall bladder without definite obstruction of the larger bile passages. The diagnoses were based on 6 operations, 5 for pathological gall bladder, 1 in a case of cirrhosis, 2 autopsies, and on clinical findings in 26 cases. These cases have been very thoroughly studied over periods of several weeks to several years. The liver was enlarged in nearly all and markedly so in about 2/3, the spleen was palpable in about 1/3, ascites was present in about 1/2, the Wassermann or Kahn was positive in about 1/4. The stools were brown in all cases at some period of the jaundice, but were clay colored part of the time in 6 cases.

In this group the tests are much less constant and definite than in the other two groups, probably as a result of the various combinations of liver cell atrophy and regeneration found in the chronic liver cirrhoses. Urobilinogen was almost invariably present and was increased in 27 cases (77%), being present in dilutions of from 1:30 to 1:500, which was interpreted as a sign of varying degrees of liver damage. In nine cases

(25%) both galactose and urobilinogen were positive. Acute infection or toxemia (alcohol, drugs, etc.) may complicate chronic liver damage in cases of cirrhosis and the urobilinogen and galactose tests become strongly positive during the jaundice, clearing up later and becoming normal, or nearly so, when the jaundice is gone. In eight cases both tests were normal.

Thus we see that almost all the cases differed from serious progressive grades of obstructive jaundice such as is found in cancer or stricture involving the common duct, by showing the continued presence of normal or increased urobilinogen. In some cases the results closely resembled those obtained in acute infectious or toxic hepatitis. In comparing the urobilinogen tests with normal persons, eight of the group were within normal limits, (0-20), four showed a slight increase (30), and the other twenty-three a decided increase (40-500). The galactose test was normal in 3/4 of the cases.

The addition of the Takata test in some of our later cases (by Dr. C. W. Heath and Dr. F. S. King) has made the diagnosis of cirrhosis of the liver much more definite. This test was used in 16 cases in this chronic group and was positive in 13. So, the laboratory finding in our cases of cirrhosis, with well-marked jaundice, are, urobilinogen usually increased (77%), galactose tolerance usually normal (75%), and Takata usually positive in well-marked cases (81%). Heath and King have already reported the results of the Takata tests.

Although there was much variation in the results

GROUP III

TABLE III

Chronic intrahepatic jaundice

Case	Age	Weeks of Jaundice	Icteric Index	Galact.	Urobil.	Takata	Diagnosis
1	48	4	50	0.4	70	+ +	portal cirrhosis
2	63	2	100	4.4	60		portal cirrhosis
3	40	2	35	1.1	20		hemachromatosis, P.M.
4	49	4	100	3.4	40		portal cirrhosis
5	45	3	25	1.2	40		Banti ?
6	45	2	15	0.2	40		portal cirrhosis
7	51	1	100	5.0	40		portal cirrhosis
8	33	1½	45	0.44	40	+	portal cirrhosis
9	3-	35	80	3.8	20		biliary cirrhosis
10	45	1	8	3.5	50		portal cirrhosis
11	47	1	75	0.5	30		portal cirrhosis
12	53	2	25	0.0	20	+ +	portal cirrhosis
13	62	3	75	0.5	20	+ + +	portal cirrhosis
14	53	4	100	1.2	30	+	luetic cirrhosis
15	48	4	30	0.4	60	+ + +	biliary cirrhosis
16	72	1	40	0.0	500	—	hepatitis, g.b., op. biopsy
17	40	½	90	0.6	125	+	*luetic cirrhosis*
18	28	8	50	1.1	125	+ +	portal cirrhosis
19	45	4	60	1.0	0	+	portal cirrhosis
20	40	2	15	1.7, 2.3	2		CCl_4
21	54	6	60	1.2	70	—	portal cirrhosis
22	32	3	105	0.6	50	—	hepatitis, g.b., op. biopsy
23	48	4	225	0.3	40		hepatitis, g.b., op. biopsy
24	4-	3	35	0.0	60	+ +	portal cirrhosis
25	52	2	15	0.0	64	+ +	portal cirrhosis P.M.
26	47	1½	13	2.5	500	+	portal cirrhosis
27	42	½	105	2.0	105		hepatitis, g. stones, op.
28	47	1	80	1.5	25		hepatitis, g.b., op.
29	21	22	70	2.0	50	+ +	biliary cirrhosis
30	47	7	60	2.2	40		portal cirrhosis
31	54	4½	60	10.2	105		portal cirrhosis
32	62	4	65	0.0	64		portal cirrhosis, op.
33	61	1	45	3.6	65		portal cirrhosis
34	52	2½	15	1.6	45		portal cirrhosis
35	45	5	60	1.8	75		portal cirrhosis

g.b.—gastrointestinal tract biopsy, op.—operation, P.M.—post mortem examination.

of the tests in this chronic group, there was usually no difficulty in diagnosis from the surgical obstructive cases of jaundice due to cancer or stricture of the common duct because of the *continued presence* of normal or increased urobilinogen and the occasional positive galactose tests in combination with some of the other clinical features of cirrhosis such as a history of alcohol, enlargment of the liver and spleen, dilated veins in the abdomen and esophagus, ascites, hemorrhage, Takata test, etc.

Only one case (No. 32) of cirrhosis was explored on account of some doubt in the minds of some of the visiting physicians and surgeons about the possibility of partial obstruction, external to the liver. Case 32 was a man of 72 with a history of lues and moderate long-continued use of alcohol. He had one course of bismuth injections five months ago. For one month there was symptomless jaundice becoming rather deep. The icteric index in the last 2½ weeks was 50-75-75-75-100-100. A firm liver was felt 5½ cm. below the costal margin. The spleen was not palpable. There was no ascites. The stools varied from light yellow to gray. There was mild anemia. A barium meal showed a small diaphragmatic hernia of the stomach. A flat plate of the gall bladder region was negative. The urobilinogen tests were 16-64-16-32-4-8. The galactose test showed no sugar excretion. A duodenal drainage showed nothing abnormal. Two Takata tests were negative. Our diagnosis was intrahepatic jaundice due to a chronic hepatitis. This was based on the alcoholic history, firm large liver, and the presence of bile in the stools, and the *constant* presence of urobilinogen in normal and increased amounts. The galactose test gave little help. Operation was considered somewhat risky on account of the probable presence of a chronic hepatitis, but was done to rule out a possible partial obstruction outside the liver which might give a similar picture. At operation a large, firm, slate-colored liver was found with an atonic gall bladder and no stones. A biopsy of the liver showed typical alcoholic cirrhosis. The patient made a normal recovery from the operation.

There were only six cases of gall bladder disease in our "painless jaundice" group in the medical wards. One is listed in the obstructive group, Case 10, a large gall stone in the common duct causing partial obstruction; five are listed under chronic intrahepatic jaundice, Cases 16, 22, 23, 27 and 28, all of which at operation showed gross chronic changes in the gall bladder and liver, also three biopsies showed a definite hepatitis. In five the urobilinogen was markedly increased and in one was normal. The galactose tolerance was normal in all. The one silent common duct stone with increased urobilinogen stands out in sharp contrast to the ten cases of malignant obstruction of the common duct and one stricture, all of which had persistently absent urobilinogen. The two tests gave no help in distinguishing the five cases of hepatitis associated with a pathological gall bladder from the other cases of chronic hepatitis. The two cases listed as biliary cirrhosis, Cases 9 and 15, were considered due to infection with B. Coli. There was no evidence of any obstruction outside the liver.

SUMMARY

TABLE IV

Well marked painless jaundice—80 cases

	Number of Cases	Icteric Index	% Positive Galact.	Urobilinogen % Present	Urobilinogen % Increased	Takata
I Acute Toxic Hepatitis	17	50-180	88	100	100	Not done
Acute Infectious Hepatitis	17	40-250	60*	94	88	Not done
II Obstructive	12	65-200	8	8	8	Not done
III Chronic Intrahepatic (Cirrhoses, etc.)	34	30-225	25	97	77	81**
Total	80					

*If five cases are omitted., three very mild and two in which the tests were made only in the convalescent period, the per cent of positive galactose tests is 83 instead of 60.
**81% of 16 cases tested.

DISCUSSION OF RESULTS

Liver function tests are disappointing at times because a damaged liver, especially a chronic one, may have normal functions of several kinds. We have simplified the problem considerably by not using a large group of function tests indiscriminately in all kinds of liver disease, to detect the presence and amount of liver damage, but in applying these two simple tests to distinguish, if possible, the different types of painless jaundice, especially the medical from the surgical.

It is obvious that the clinical grouping of cases of jaundice as intra hepatic or obstructive is somewhat arbitrary. While diffuse liver cell damage is the characteristic finding in acute infectious hepatitis (catarrhal jaundice) there are some which show obstruction of biliary capillaries by bile thrombi or cholangitis in the early stages, and, conversely, there is some liver cell damage in all prolonged biliary obstruction outside the liver, and in the cirrhoses we have a combination of varying degrees of atrophy and regeneration. The tests are most useful where one type of pathology predominates, as it so often does, and we make the diagnosis of this predominant factor.

The results of the tests are shown on Tables I, II, III and IV. In well-marked infectious and toxic hepatitis during the height of the disease the urobilinogen was nearly always present (94 to 100%), and nearly always increased (88 to 100%). The galactose was positive as a rule (83 to 88%).

In marked obstructive jaundice, due to cancer or stricture or impacted stone in the common duct, the

urobilinogen was nearly always absent (92%); the galactose was nearly always normal (92%).

In chronic intrahepatic jaundice (mostly cirrhoses) the urobilinogen was nearly always present (97%) and increased as a rule (77%). The galactose test was positive in 25% of the cases. In sixteen of the cases of cirrhosis in this group, the Takata test was done by Drs. Heath and King. Thirteen were positive (81%) and three negative. The six gall bladder cases, all with associated hepatitis, could not be clearly distinguished by the tests from other types of chronic hepatitis. The urobilinogen was increased in five, normal in one. The galactose was normal in all.

Our results in well-marked cases of painless jaundice agree in general with those of Bauer and most other recent authors such as Woerner, Wallace and Diamond, Jolliffe, Piersol and Tumen, Shay and Schloss, Davies, Rosenberg, Schiff and Senior. The tests were positive as a rule where acute, diffuse cell damage predominates, as in catarrhal jaundice and toxic hepatitis. A positive galactose test (with diabetes ruled out) means liver degeneration and the excretion of large amounts, 6-7 grams, is practically conclusive. The tests were negative as a rule where there was gross mechanical obstruction of the common duct. In the cirrhoses we disagree with Bauer who says that "*almost all cirrhoses show a strongly positive galactose test.*" In our cases only one-fourth were positive.

Banks, Sprague and Snell found more positive galactose tests in the obstructive group than we did and explain this by the presence in their series of many severe cases of long duration with advanced destruction of the liver parenchyma, so that the liver reserve had been overcome and regeneration had failed.

Table IV gives a summary of both tests in the three groups of cases. In comparing the cases of group 1, acute diffuse liver cell damage, with the cases of group 2, subacute obstruction outside the liver due to cancer or stricture of the common duct, both tests were very different as a rule. The galactose being almost always positive, and the urobilinogen almost invariably present in increased amounts in group 1, and the galactose being almost always normal and the urobilinogen almost invariably absent in group 2.

In comparing group 2, the obstructive cases, with group 3, the cirrhoses, the galactose test gave little help. The urobilinogen test was very different as a rule, being almost invariably absent in group 2 and practically always present in group 3, and in increased amounts in over 3/4 of the cases.

The important feature is the separation of medical *from surgical cases of painless jaundice.* We have avoided sending several middle-aged cases of subacute hepatitis to the surgeon for exploration. We certainly hesitate to advise exploration in such patients if both galactose and urobilinogen tests are strongly positive and the stools are brown.

We have also been able to urge the surgeon to operate on several obstructive cases which he believed were chronic hepatitis. We have definitely improved our differential diagnosis of medical from surgical jaundice, and of fifteen cases sent to the surgeon, only one went with a wrong diagnosis. The onset of catarrhal jaundice was discovered once by the urobilinogen test before the jaundice appeared.

All liver function tests are affected much more by diffuse changes of the whole liver even though slight, than by complete destruction of quite large portions of the liver if the remainder is normal (tumors, etc., not involving bile ducts). As in the kidney, there may be resting units which can be used in an emergency. Thus, we may expect changes in liver function only when practically all the liver cells are acutely damaged, or when chronic liver disease has gone so far that few or no normal cells are left and regeneration has failed.

Vigorous regeneration of liver cells in the convalescence from acute disease and in the remissions of chronic disease give us normal metabolic tests. In obstructive (and hemolytic) jaundice enough normal liver tissue is left, in the earlier stages at least, to carry on carbohydrate metabolism and the galactose test is usually normal.

It is not wise to base diagnosis on single tests which may be misleading on account of constant changes in liver function during an acute or subacute illness. For example: urobilinogen is usually absent in the acholic stool period of acute infectious and toxic hepatitis, although usually strongly positive at other times. The test is also usually normal in the late convalescent period of mild acute hepatitis and in chronic hepatitis in a period of compensation. The urobilinogen test may be positive or normal in the early stage of malignant obstruction of the common duct, although persistently negative later. *A course of tests* on the other hand will usually give the whole picture, and avoid mistakes.

We found the urobilinogen test useful, simple and inexpensive. A series of tests could easily be run every day or two for one or two weeks. It proved the more sensitive test of the two. For example: in five of our cases of acute infectious and toxic hepatitis (including most of the mild ones) the urobilinogen test was positive while the galactose test was normal. The same was true in 18 cases of chronic cirrhosis of the liver. It appears to be a very delicate test of liver dysfunction but is, however, low or absent in cases where very little or no bile reaches the bowel such as obstructive jaundice or for a short period (a week or less) in the early stages of acute infectious or toxic hepatitis. It is probably more often useful than the galactose test in differentiating intrahepatic from external obstructive jaundice, and occasionally some factor such as dehydration, oliguria or inability to take the dose on account of vomiting may make the galactose difficult to use or to interpret, but the combined use of the tests is on the whole best of all.

There was a minor difficulty in interpreting the tests in a few cases. The more definite the test the better; for example, if the galactose excretion is 1 gram in one case and 6 grams in another we have no hesitation in pronouncing one normal and one abnormal. But, if the excretion is between 2.5 and 3 grams the interpretation of the result is not easy, and the test should be repeated. We found few such borderline cases, and, of course, we had the urobilinogen test as an additional help. A large amount of galactose, 5 or 6 grams or more, is clear evidence of liver cell injury though normal galactose does not exclude it.

There was evidence of dissociation of liver functions. There was no definite relation between the degree of jaundice and the degree of galactose tolerance. When an acute or subacute disturbance is clearing up the galactose tolerance usually reaches normal before the icteric index. Althausen has suggested that this high index with normal liver function may be due to bilirubin which has been stored in the tissues, and is

being carried by the blood to the liver for excretion. Occasionally, the icteric index may be low while poor galactose tolerance persists.

The tests have some value in prognosis not only by showing the extent of the dysfunction, but also by following the course of the illness and showing whether the liver damage persists or is increasing or lessening. The urobilinogen test may remain positive after all other signs are gone in acute toxic or infectious hepatitis, showing some residual liver damage.

The urobilinogen test is a guide to the diffuse liver injury which may occur in an attack of cholecystitis. The urobilinogen may increase to 40 or 50 during the attack, and then drop to normal within a week after the attack is gone. Watson has shown the same effect on the urobilin excretion in attacks of cholangitis associated with a ball value stone in the common duct.

In gall bladder cases, with or without partial obstruction of the common duct, the tests were not distinctive. Some were normal, some were abnormal, depending, apparently, on the amount of associated hepatitis or infection. The tests gave little help in distinguishing this type of case, which is often surgical, from the medical cases of acute and chronic hepatitis. Fortunately, silent stones in the common duct are rather uncommon and we may expect to get evidence in most gall bladder cases in other ways—by the history and ordinary physical examination, by the X-ray and the duodenal tube.

A study of the exceptional results was profitable. They may be due to the variability of the tests, the period of the disease, or its character (the simultaneous presence of obstruction and liver cell damage). The diagnosis is best made not by early impressions and early tests, but usually, in a difficult case, from the clinical course over a period of intensive study of a week or two.

The time of the test in relation to the period of the disease is very important. Mild and convalescent cases are apt to have normal tests; fortunately, they are less important in diagnosis. The amount of functioning tissue in the liver is constantly changing and tests should be made at the height of the jaundice or just before this to have their full value. In an exceptional case of intense acute hepatitis with deep jaundice, both tests may remain normal during the period of observation of 10 days to 2 weeks; the urobilinogen perhaps because very little or no bile reaches the bowel, and the galactose for some reason which we cannot altogether explain, perhaps the remarkable functional reserve of the liver.

Our cases of marked obstructive jaundice, due to cancer or stricture involving the common duct, have reacted to the tests in a definite and uniform manner with only one exception. Some positive galactose reactions seem inherent in the nature of the test and were probably due to the presence of serious functional liver cell damage in this case of severe and long standing obstruction. The per cent of positive galactose tests in this group (9% in our series) will depend considerably on the number of this type of case which is included in it. Perhaps a longer experience may show a greater per cent, as has been reported by Snell; however, the constant absence of urobilinogen, especially in the case of malignant obstruction, has given valuable help in making the correct diagnosis.

In cancer involving the common duct the interval between the onset of jaundice and complete obstruction of the duct is short, usually only 2 or 3 weeks because the first appearance of jaundice means decided narrowing of the duct. In cancer this complete obstruction is due to rapid constriction and closure of the common duct, while in stone there is no constriction, the duct dilates above the stone and some bile goes by.

Two rare exceptions to this rule have been seen since first writing this paper. One patient (B.B.) aged 76, had a small soft pedunculated adeno-carcinoma in the common duct causing only partial obstruction with cholangitis and multiple abscesses in the liver. Urobilinogen was always present in the urine and usually high. Conversely, one patient (J.J.) aged 52, had gall bladder disease and the hepatic and common ducts were solidly plugged with putty like material and gravel, causing complete obstruction and entire absence of urobilinogen in the urine in 5 tests.

Partial obstruction external to the liver due to common duct stone, especially when complicated with infection and hepatitis, may be difficult or impossible to distinguish by these tests from the jaundice due to pure chronic diffuse disease of the liver such as the cirrhoses. The urobilinogen and galactose tests may be normal or increased in both and the diagnosis must be based on other clinical data. Thus some gall bladder cases, which are often surgical, may not be distinguished by these tests from the medical cases of acute and chronic hepatitis. This difficulty occurred only once in our series, in case 10, group 2, a large gall stone in the common duct. The correct diagnosis was made from other clinical data. One case of cirrhosis, case 32, group 3, was explored because the possibility of partial external obstruction was seriously considered.

Improvement in the diagnosis of these cases of jaundice may be due in part to greater interest and more intense clinical study as well as to the use of special tests, but we believe the latter have real importance. The better the clinician, the better he will be able to interpret the tests and to combine them with the rest of the clinical picture.

SUMMARY

The urobilinogen and galactose tolerance tests in the urine were used in 80 cases of painless jaundice in the medical wards. Of seventeen cases of acute infectious hepatitis, urobilinogen was present in sixteen and increased in fourteen. Ten gave a positive galactose test. The negative results occurred largely in the very mild cases or in those tested only in the convalescent period. In twelve well-marked cases tested during the height of the jaundice, the galactose was positive in ten and the urobilinogen increased in ten. In seventeen cases of acute toxic hepatitis, the urobilinogen was increased in all and the galactose positive in fifteen. In twelve cases of jaundice due to obstruction outside the liver, urobilinogen was absent in eleven and increased in one, the galactose normal in ten and positive in one.

In thirty-four cases of chronic hepatitis, mostly cirrhoses, urobilinogen was present in thirty-three and increased in twenty-seven. The galactose test was positive in nine. Both tests were normal in eight cases. In sixteen well-marked cases of cirrhosis the Takata

test was positive in thirteen. In six gall bladder cases, all with associated hepatitis, the urobilinogen was increased in five and normal in one. The galactose was *normal in all.*

The tests were positive as a rule where diffuse liver cell damage predominates as in catarrhal jaundice and toxic hepatitis. A positive galactose test in painless jaundice (with diabetes ruled out) means liver degeneration, and the excretion of large amounts, 6-7 grams, is practically conclusive. The tests were negative as a rule where there was malignant obstruction of the common bile duct. In painless jaundice the important diagnosis is between the medical and surgical type. This is especially true in middle life when cancer is *frequent.* The combination of these two simple tests in the urine for urobilinogen and the galactose tolerance has proved a useful aid in distinguishing several groups of medical and surgical cases; namely, acute and chronic, toxic and infectious hepatitis from painless obstruction outside the liver.

One of the most important findings was the persistent absence of urobilinogen in obstructive jaundice *due to cancer of the head of the pancreas* or common bile duct. Persistent acholia of the stools developing rather early, after two or three weeks of jaundice, with *persistent absence of urobilinogen* in the urine, appears to be the rule in malignant obstruction and rarely occurs in other forms of jaundice. In acute hepatitis it is only temporary, and in the obstruction due to stone is rarely complete. In our one case of silent stone in the common duct the *constantly increased* urobilinogen was in sharp contrast to its *persistent absence* in the ten cases of malignant obstruction

In gall bladder cases, in general, which are often surgical, the tests were not distinctive. They depended, *apparently, on the amount of associated hepatitis* or infection and resembled those in the medical cases of acute and chronic hepatitis, and the diagnosis was made from other clinical data. Occasionally there may be great difficulty in distinguishing painless *partial* obstruction of the common bile duct with secondary damage to the liver from a primary subacute or chronic diffuse disease of the liver. This occurred once in our series

On account of the variation in liver function at different periods of an attack of jaundice and some variation in the tests themselves, it is not wise to base diagnosis on a single test. A course of tests, beginning early if possible and carried through the height of the jaundice for a week or two, is far more valuable.

A positive galactose test in painless jaundice indicates liver degeneration, a normal test does not always exclude liver cell injury. The urobilinogen test has value in showing the presence or absence of bile in the bowel, as well as being a very sensitive indicator of *liver disturbance. It is a more definite guide to liver* dysfunction than the galactose test (if hemolytic jaundice is excluded) and is more often useful in distinguishing intrahepatic from external obstructive jaundice, but a combination of the two tests is best of all.

The tests have a definite value in prognosis by measuring the speed and degree of recovery of liver function after an attack of jaundice. The urobilinogen and galactose may remain positive long after active symptoms have disappeared showing residual liver damage. In an occasional borderline case the tests may be inconclusive, or even misleading.

Finally, these simple tests have proved useful aids and have definitely improved our differential diagnosis of painless jaundice, and deserve to be used more in this particular field.

CASE REPORTS

The following case reports illustrate the application of the tests in diagnosis; only relevant data are given: The first case shows how one test backs up the other and the value of the galactose test at a time when no bile was reaching the bowel.

1. (*Case 5—Infectious Hepatitis*). *J. D. A.*, a man of 45, had for ten days a gradually increasing symptomless jaundice with loss of 8 pounds in weight. Physical examination showed nothing important. The icteric index was 200 on admission and rose to 250. The stools remained clay colored during the first week of observation. The white blood cells were 6300. There was slight anemia. Roentgen rays of the stomach and bowel after a barium meal, also a flat plate of the gall bladder region, showed *nothing* abnormal. Four urobilinogen tests in the first week were negative. The first impression was obstructive jaundice due to cancer of the head of the pancreas or a possible silent stone in the common duct. The galactose test, however, showed 6.8 Gm. output and surgical treatment was put off and the diagnosis of infectious hepatitis (catarrhal jaundice) was suggested. This was confirmed by the subsequent course. At the end of a week the stool began to show some brown color and the jaundice to lessen, the index dropped from 250 to 50 in the next 11 days. The urobilinogen rose to 45 and gradually dropped to *normal* at the end of four weeks from admission. At the end of 2½ weeks the galactose test had become normal showing no excretion of sugar. Recovery was uneventful.

The second case illustrates the course of the tests in a *fairly typical case of well-marked infectious hepatitis* (catarrhal jaundice).

2. (Case 7—Infectious Hepatitis). *E. J.*, a rather plump woman of 40 years, with three children, complained of malaise for one week followed by jaundice for one week. There was some nausea and gas with rare vomiting and a dull ache in the right side of the abdomen. The edge of the liver was just felt. The spleen was not palpable. X-rays of the gastro-intestinal tract and gall bladder *region were negative.* The stools were pale yellow with a *positive* Benzidin test for blood. At entrance the icteric index was 75, the urobilinogen 80 and the galactose excretion 4.8 Gm. The icteric index rose to 140 and then gradually dropped to 10 at the end of three weeks. The urobilinogen readings were 80, 90, 80, 60, 30, 10 in the *same* period. At the end of three weeks the galactose excretion was 2.7 Gm. The patient made a gradual but uneventful recovery. A Graham test of the gall bladder after the *jaundice* was gone gave a normal result.

The third case is a good example of a severe *toxic* hepatitis masquerading as obstructive jaundice.

3. (Case 10—Toxic Hepatitis). *T. S.* This 72 year old woman was admitted with a story of 10 days' jaundice. She was very ill and the history incomplete, *recent* dyspnea and edema of the feet, and for several weeks anorexia, regurgitation of food and some vague epigastric distress. The *icteric* index was 200; she had an arteriosclerotic heart, the liver was not palpable, there was tenderness in the epigastrium, and a question of a mass in the gall bladder region. The temperature was normal to 99.8°. The white blood count 11000 to 9000; the stools gray with a tinge of brown. Our first impression was an obstructive jaundice, but several urobilinogen tests were 40 and the galactose excretion 3.6 Gm. Both tests pointed toward intrahepatic rather than obstructive jaundice. Finally a *history* was obtained from the family of recent joint pain

and the use of cincophen tablets two or three times a day for a month. The diagnosis of toxic hepatitis was then definitely established. The stools became brown and the urobilinogen remained above normal. The patient became comatose and in spite of the liberal use of glucose intravenously and by Murphy drip died ten days after admission. The liver weighed 970 Gm. with marked toxic central necrosis and small scattered areas of regeneration. *Diagnosis*, subacute yellow atrophy of the liver.

Number four illustrates the use of the tests in a case called "catarrhal jaundice" by the surgeon.

4. (Case 1—Obstructive Jaundice). *A. D.*, was a man of 55 with a story of former rather excessive use of alcohol. He had jaundice for 2½ weeks with mild abdominal cramps and three loose stools at the onset, none since. Some epigastric fullness and "gas." Loss of 10 pounds in the last two years. Physical examination showed nothing important except arteriosclerosis and hypertension. Icteric index, 100. Stool, light yellow, later gray. Benzidin test for blood, moderately to strongly positive. Temperature, normal. Red blood cells, 4,030,000. White, 4250. Hemoglobin, 75%. Barium meal and enema showed nothing abnormal. Urobilinogen, 0. Galactose, 0.51 Gm. The tests favored the diagnosis of obstructive jaundice. The surgeon who saw him suggested "catarrhal jaundice" and advised further observation. The stools continued clay colored. The urobilinogen tests were entirely negative for another week and a second galactose test was normal. Exploration was urged with the diagnosis of obstructive jaundice due probably to cancer of the head of the pancreas. At operation this was found.

Number five illustrates the use of the tests in the differential diagnosis between portal cirrhosis and obstructive jaundice.

5. (Case 4—Obstructive Jaundice). *S. D. P.*, age 59. This man had drunk a bottle of wine daily for many years, was usually well, but had jaundice for three weeks with loss of 7 pounds of weight, and a dull ache in right upper quadrant extending to the back. Stools and urine were "yellow." Abdominal examination showed a firm, smooth liver one or two fingers breadth below the right costal margin with a smooth projection on the right side which was considered a Riedel's Lobe or possibly a distended gall bladder. The icteric index was 75. The stools, light yellow. The temperature normal. The urobilinogen, 0. The galactose excretion, 0.8 Gm. The surgeon made the diagnosis of alcoholic portal cirrhosis and suggested further observation. Five urobilinogen tests were entirely negative, (one showed a green color), and the stools became clay colored and remained so. We felt that the tests strongly favored obstructive jaundice, particularly the uniform absence of urobilinogen in the urine, and urged exploration. A cancer of the head of the pancreas was found.

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Production of Peptic Ulcers in Rats and Mice by Diets Deficient in Protein*

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ULCERATION OF THE PROSTOMACH

BUCHNER, Siebert and Molloy (1) found that *ulceration* of the prostomach occurred in some rats that were starved every other day during a period of 17 days. More striking ulceration was produced when rats subjected to such a regimen were given histamine on starvation days. Bürkle-de la Camp (2) confirmed the findings of Büchner, Siebert and Molloy with intermittent starvation plus histamine but he did not observe ulcers in rats that were starved during single periods of five days or less. The possibility of ulceration following starvation was of particular interest to one of us (F. H.) because of personal experiences which included fasting every other day for five consecutive months and single fasts of as long as 41 days. Moreover, the 41-day fast and a 33-day fast were undertaken as part of studies of the effect of variations in the protein intake on the fasting gastric acidity (3b) and hunger sensation (4). In these studies, it was found that the fasting gastric acidity was increased by protein restriction and after fasting and that a peculiar and intense hunger sensation developed which was regarded as a protein-hunger sensation. The fasting gastric acidity again decreased and the protein-hunger sensation disappeared with protein realimentation. If these findings on man also applied to rats, it seemed that the amount of ulceration that was likely to occur in rats, solely as a result of intermittent starvation, would depend considerably upon the amount of protein in the diet fed on feeding days. Besides this, it seemed possible that ulcers might develop in rats as a result of sufficiently prolonged

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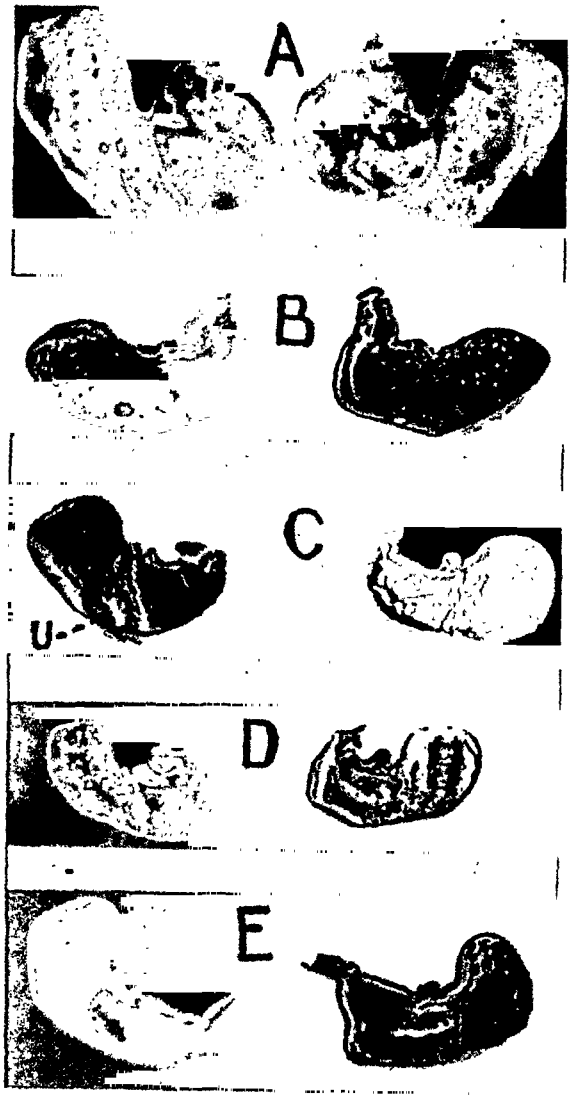


FIG. 1. Showing gastric ulceration in rats starved or fed diets deficient in protein. A, male starved 2× days, then fed adequate diet 28 days, next starved 2× days, then fed again 35 days and finally starved to death in 3× days; final age 4×2 days and weight 178 gm.; marked ulceration of prostomach with some extended perforation and stricture of pylorus and erosion of main stomach. B, female, fed only white bread 27 days, last after 24 hrs before death; ate all but half of one, last 2 weeks kept in hot environment, marked ulceration of prostomach with little bleeding. C, female, 16 days on diet of 100 parts lard, 10 parts dried yeast, 4 parts salt mixture and 100 parts cellulose flour, next after 19 (terminal) on 5th day prostrated, appeared to be terminal when sacrificed; perforated ulcer. U, penetrating into liver. D, male, died after 12 days starvation. Early appearance of lesions (at) after that temperature 12° C.) was still too low to prevent serious feeding. E, female, starved 2× days, then fed 20 days, next starved 2× days and then sacrificed after 6 days on adequate diet, showing healing of ulcer well on its way.

starvation or protein restriction alone and ulceration thus produced could evidently be regarded as objective evidence of protein-hunger carried to a pathologic extreme.

As already indicated in a preliminary report (5a), we tested our first inference experimentally by starving 35 rats every other day or during alternate two-day periods and feeding some of the rats diets adequate in protein and others diets low in protein on feeding days. As a result, some rats developed ulcers in the prostomach within three weeks even when a diet adequate in protein was fed on feeding days but all rats that were intermittently starved and fed diets with only about 3% protein for more than two weeks developed ulcers in the prostomach. No ulcers were found in the prostomach of 175 stock (control) rats.

These results led us to extend our study to determine the effect of more prolonged starvation, protein restriction without starvation, diets high in protein, diets differing in the main type of protein used, high and low carbohydrate or fat diets, watery diets, diets deficient only in vitamin A or B, and diets to which salt, pepper, mustard, acetic acid, alcohol, hydrochloric acid or antacid salts were added. The effect of adding various kinds and amounts of roughage to some diets was also investigated. In addition to this, the effect of exposure to high and low environmental temperatures was observed. More recently, tests were made to determine the value of histidine (Larostidin) as a preventive of ulceration. In nearly all cases 8 or more rats were used for each specific test. Altogether 1704 rats and 77 mice, including 230 stock (control) rats and 7 stock mice, were used. Most of our rats were white rats but 73 were black-and-white.

Prolonged starvation (with water given) proved to be our most effective method of producing ulcers in the prostomach of rats (Fig. 1-A, D and E). Some ulceration was usually observed when rats were sacrificed after 4 days of starvation but great individual variations occurred. In a few adult rats ulcers were not present after 7 days of starvation while in one young rat well developed ulcers were found after only 36 hours of starvation. The impression was that diets entirely devoid of protein would produce ulceration about as easily as starvation but we used powdered yeast as the source of vitamin B in our synthetic diets and, when such diets included 5% or 6% yeast to make them substantially adequate in vitamin B, they contained from 2% to 3% yeast protein (which is rich in essential amino-acids). All of 10 rats fed a diet with 6% powdered yeast as the sole source of protein, but otherwise adequate, had ulcers in the prostomach when they were sacrificed after from 13 to 21 days. Diets containing larger amounts of yeast caused less ulceration when fed for only 2 or 3 weeks. Five out of 12 rats had ulcers in the prostomach after having been fed 14 days with a diet containing 20% gelatin as the chief source of protein but otherwise quite satis-



FIG. 2. Section through large prostomach ulcer with adhesion to and penetration into liver, shown in Fig. 1—C, U. E, edge of epithelium of prostomach (healing some overgrowth).

factory. Nineteen out of 27 rats fed only white bread (which contains about 10% protein) showed ulceration of the prostomach within 4 weeks. Rats that did not get ulcers from a diet of white bread usually ate more and thus ingested more protein than rats that developed ulcers. On the other hand, rats that developed ulcers on diets adequate in protein ate very little. This occurred when the diets were deficient only in vitamin A or B but such diets did not lead to ulceration as soon or as uniformly as diets deficient in protein. Diets low in protein caused ulceration whether high in carbohydrate or high in fat. Some rats manifested an apparent nausea after ingesting diets high in fat and low in protein—they gagged and salivated after eating as if about to vomit. Such reactions were never noticed when diets high in fat but adequate in protein were ingested. Wet low-protein diets (thin pastes made by adding large amounts of water to dry food or diets of fresh vegetables only) caused little or no ulceration even when fed as long as 7 weeks, although ascites was produced in most cases. The addition of table salt to such or other diets did not cause any definite increase in ulceration. Mustard added to a deficient diet, such as a white bread diet, seemed to make it more adequate or more palatable to rats. Pepper added to diets led to a reduction in the food intake but the ulceration which followed could not be ascribed to irritation by the pepper. Hydrochloric acid as well as sodium bicarbonate added to diets usually led to a reduction in the food intake but the acid produced more acute erosion and ulceration and the alkali led to some hyperkeratinization about the ulcers that developed in the prostomach. Alcohol added to the diets caused pylorospasm and gastric retention with ulceration (5c, d). The most striking ulceration occurred when pregnant rats were fed diets deficient in protein (Fig. 1-B, C and Fig. 2).

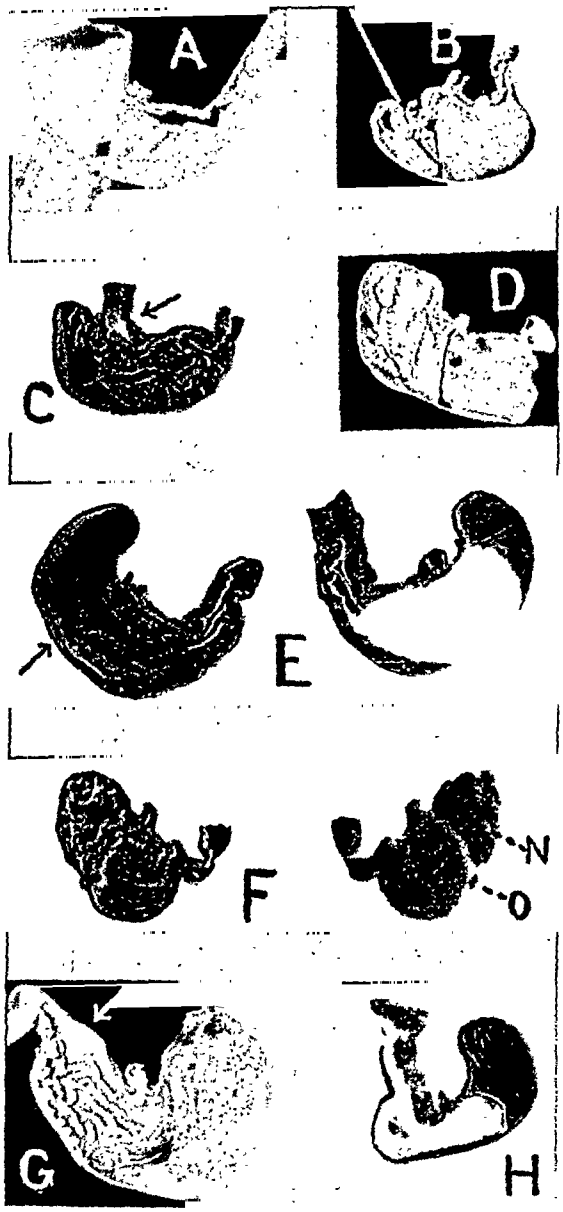


Fig. 3. Showing various gastric lesions in rats. A, male, starved 7 times from 8 to 18 days, total 94 days, last 18 days high fat and adequate protein diet with dog hair, sacrificed; perforated ulcer with adhesion to abdominal wall, hair in this ulcer and in cornified nodules nearer cupola of prostomach. B, female, died after 10 days starvation following 13 days white bread diet; ulcer in cupola perforated with invagination and thickening of prostomach. C, male, sacrificed after 5 months on white bread, last 3 months with cellulose flour; marked ulceration of esophagus, hypertrophy of mucosa of main stomach due to use of bulky material. D, male, died without showing interest in eating after 8 days starvation following 40 days on white bread with cellulose flour; ulceration probably parrlyzed functioning of stomach. E, female, sacrificed after 5 months adequate diet with dog hair; raised 3 litters in nests of dog hair; dog-hairball practically fills stomach; arrow indicates small ulcer due to greatly decreased food intake. F, inner and outer aspects of ventral half of stomach; female, starved 8 times from 5 to 7 days, final 32 days diet high in fat, low in protein (6%) and with dog hair, died; O, large epithelial cyst; N, cornified nodule—section shown in Fig. 4—B. G, male, starved 9 and 10 days, then 2 months diet high in protein plus HCl, sacrificed; severe diffuse erosion of prostomach (due to HCl) and multiple craters in antrum. H, male, 2 months on washed bran plus casein and gluten, final month kept cool, died; diffuse erosion with bleeding of main stomach.

Pappenheimer and Larimore (6) found that 61% of rats fed a diet containing 95% white flour developed ulcers in the prostomach but they apparently did not suspect that the protein inadequacy of the diet, of which they were fully aware, could be responsible for the ulceration. They attributed the ulceration to mechanical irritation or infection by ingested hair. We found hair in the stomachs of many rats and well formed rat-hairballs in 13 rats without any relation to ulceration. We also added cut up, coarse dog hair to the diets of some rats and thus produced dog-hairballs in the stomach of 3 rats but, with a diet adequate in protein, a shallow ulcer developed only in one case where the dog-hairball became so large that it finally interfered with the food intake (Fig. 3-E). However, when dog hair was fed with a diet deficient in protein, hair sometimes penetrated into the denuded (ulcerated) areas. In a few rats that were later again fed diets adequate in protein some ulcers healed with bristling stubs of dog hair healed *in situ*! McCarrison (7) observed gastric ulcers in rats fed diets such as were used by certain natives of India among whom peptic ulcers frequently occurred. These diets were low in protein. A number of other investigators reported that gastric ulcers developed in rats as a result of vitamin deficiencies but, as already suggested, our observations indicated that ulceration under such circumstances is due to a lowered food (protein) intake. Peptic ulcers also must have developed in many instances in rats and mice used in studies of the biological value of proteins, particularly of proteins markedly deficient in some essential amino-acids, but ulcers were evidently not even looked for. The question now is: Are the apparently essential amino-acids essential

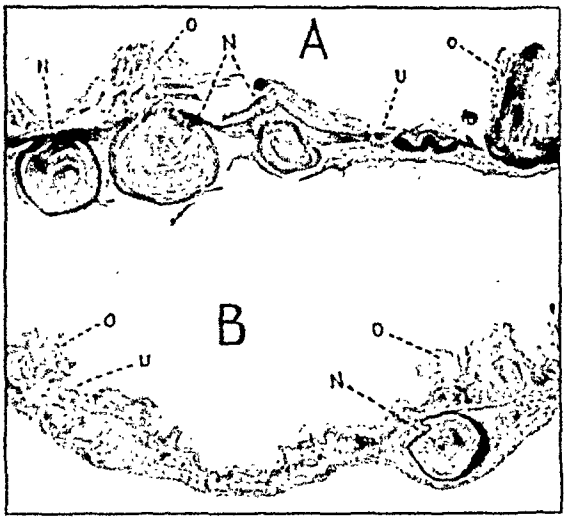


Fig. 4. Sections showing marked morphological changes following ulceration in prostomach of rats. A, female, black-and-white, died after 58 days on white bread with cellulose flour; with numerous cornified nodules (N) mainly in cupola of prostomach; O, epithelial overgrowth, U, ulcer. B, section through nodule (N) shown in Fig. 3—I; white rat.

primarily for growth, as has heretofore been assumed, or are they essential primarily to assure a quantitatively adequate food intake by preventing peptic irritation or ulceration?

The environmental temperature was found to be an important factor in determining the degree of ulceration that was likely to occur in starving and malnourished rats. The desirability of a relatively high temperature for the comfort of starving and undernourished animals was already appreciated by the senior author of the present report because of disagreeable personal experiences while fasting or using restricted diets during cold weather. Accordingly, a room was fitted with electric heating units to supplement the regular heating facilities and to automatically maintain temperatures at the desired levels. Starving animals were usually kept in this room at from 28° C. to 31° C., depending upon their condition. For experimental control, some rats were also kept in a modified ice box, especially during hot weather, to note the effect of relatively low temperatures (15° C. to 20° C.). It was found that starving rats died much sooner in a cool environment than when they were kept warm. A cool environment or chilling caused diffuse peptic erosion and increased the bleeding of lesions in the stomach. In terminal stages, it also caused diffuse bleeding mainly in the middle half of the small intestine, without previous erosion or ulceration. Besides this, chilled rats passed bloody urine. On the other hand, little or no serious bleeding occurred in the digestive tract of rats that were kept warm. At 28° C. to 31° C., we were able to starve rats from 15 to 39 days on 42 occasions, with more striking ulceration than could have been obtained at lower temperatures.

The lesions that develop in the prostomach of rats have already been described in more or less detail by others (1, 2, 6) and we agree with the German investigators (1, 2) that peptic erosion by acid gastric juice is responsible for such ulceration. Figures 1, 2, 3 and 4 show various types of prostomach ulceration. It will be noted that the largest prostomach ulcers or the most severe ulceration (including perforations in 4 of our rats) occurred on the ventral half of the stomach near the ridge dividing the prostomach (the non-acid-secreting part of the stomach) from the main stomach or ventriculus (the acid-secreting part). The ventral half (the halves on the left in Fig. 1) is the lower half of the stomach in the position most commonly assumed by rats. Gastric residues would therefore tend to gravitate into and remain most directly in contact with this part of the stomach. The cupola, dome or fundic portion of the prostomach was also highly vulnerable (perforations in one rat — Fig. 3-B — and in one mouse). Ulceration often occurred on the ridges of the rugae formed by the contracted stomach (Fig. 1-D) but the stomach was usually relaxed in rats that had been kept warm. Ulceration about the esophagus was also common (Fig. 3-C and Fig. 5-A). In fact, the entire prostomach of rats and mice might be regarded as a dilated portion of the esophagus which is considerably exposed to the acid gastric juice when the food intake is inadequate.

LESIONS OF THE MAIN STOMACH

Ulceration of the main stomach of rats was not as easily produced as ulceration of the prostomach and the lesions that developed in the main stomach were different. Thus among the 175 control rats referred to earlier in this paper, 3 rats had "craters" in the antrum although none of them had ulcers or other lesions in the prostomach. But such "craters" (Fig. 3-G) can hardly be regarded as ulcers. We have, however, come to recognize them as an early stage of the most common type of ulceration in the main stomach, antrum and prepyloric region of rats. These lesions simply have a crater-like appearance and usually consist of a slightly elevated and pale or white (mucus-secreting ?) ring from 1 to 2 mm. in diameter with a "pin-point" depression in the center. Sometimes the depressions were not evident and sometimes numerous depressions appeared without surrounding rings or crater-like rims. Under the microscope, sections of typical craters generally showed only a depression in an otherwise intact mucosa but, with transillumination, the pin-point depressions looked like potential perforations (Fig. 5-E, F). The centers of some craters usually bled when bleeding did not occur elsewhere after the animals had been chilled.

Starvation and diets with less than 4% protein, which often gave rise to marked ulceration in the prostomach, usually caused only a little erosion in the main stomach and rarely gave rise to crater formation. This may have been due to the fact that it generally took longer for craters to develop in the main stomach than it took for rats to die from starvation or from extreme protein restriction. However, a diet of white bread (the protein of which is deficient chiefly in lysine) led to prepyloric crater formation in about 70% of the cases in 2 or 3 weeks. When white bread was fed exclusively for about 4 weeks or longer, the centers of some of the craters were usually more or less eroded and presented the appearance of ulcers. The addition of 25% or more of cellulose flour to diets somewhat inadequate in protein often increased crater and ulcer formation (Fig. 5-A and Fig. 6-A). The craters found in the 3 control rats referred to above were very likely due to the feeding of too much bread

or corn. Our observations also showed that a diet with gelatin as the main source of protein has a marked tendency to initiate the development of craters in the acid-secreting part of the stomach.

A particularly striking type of lesion of the main stomach was a "punched in" ulcer-like lesion (Fig. 5-B) seen in two rats that were fed only white bread while pregnant. Such lesions probably correspond to the punched out round ulcers that have been produced in dogs but, in our rats, the areas surrounding these lesions were markedly discolored (blue or purple) and this suggests that circulatory disturbances occurred in these areas. However, we believe that the apparent interruptions in the circulation in these areas were a consequence and not the cause of these rapidly developing lesions. Sections under the microscope again showed that the mucosa was also intact in and about these ulcer-like lesions. This and the histological findings concerning the more common craters referred to in the preceding paragraph support the frequent claim that gastric ulcers, such as are seen in humans, do not begin as erosions of the mucosa. Further study is needed to determine whether the mucosa remains intact while a considerable amount of tissue beneath it is destroyed or whether it alternately erodes and heals.

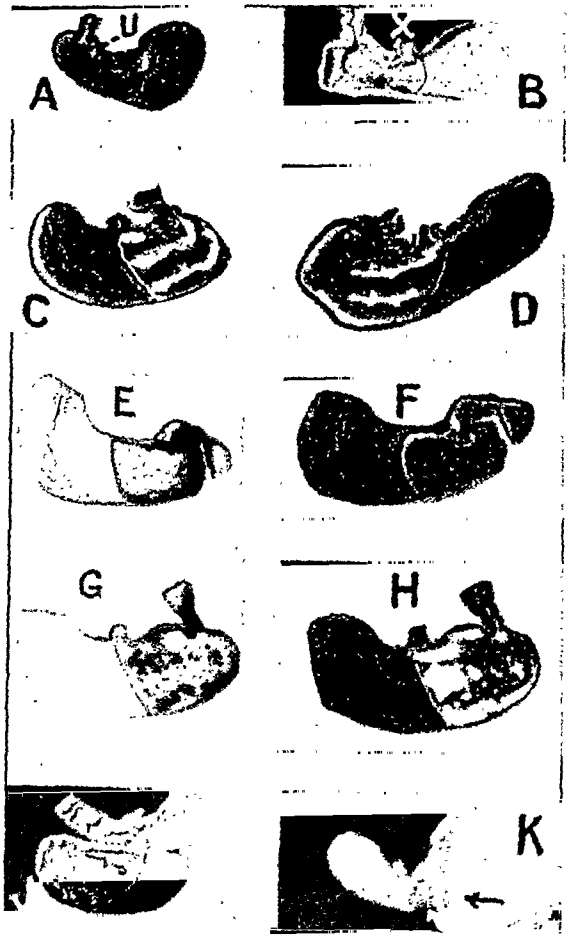


Fig. 5. Showing chiefly lesions in main stomach of rats. A, female, fed white bread with cellulose flour 14 days, sacrificed; U, ulcer in antrum at incisura—section shown in Fig. 6—A; also large ulcer at oropharynx. B, female, fed only white bread 31 days; cast litter (removed) 4 days before death, X, "punched in" ulcer-like lesion in discolored area on rugæ in center of main stomach. C, male, fed diet 3 weeks with 43% casein plus cellulose flour and HCl, last 6 days in cool environment, died; roughening of prostomach (due to acid) and marked erosion of rugæ in main stomach. D, male, fed mainly bran 6 weeks, last 3 days cool (15° C. to 23° C.), died; marked erosion of rugæ and numerous pin-point depressions in main stomach. E, transillumination of F, male, 3 months low protein diet—mainly white bread and cellulose flour, last month hot weather and given some alcohol; numerous pin-point depressions in main stomach—seen best by transillumination. G, transillumination of H, female, 6 weeks high protein diet with cellulose flour, last 6 days cool, died; erosion and bleeding of main stomach with pin-point depressions and fissuring—more evident by transillumination. J, male, 6 weeks coarse washed bran plus mainly carbohydrates, last 7 days kept warm, died; scooped out lesions in main stomach without much bleeding. K, young female, died after 36 hours starvation, final weight 34 gm.; diverticula in antrum similar to diverticula found in other young rats fed mainly bran.

The study of the development of lesions in the main stomach of rats is additionally complicated by the fact that diets relatively high in protein (with about 35% or more of protein) usually cause inflammation and other injuries, especially when coarse materials are fed. Bran had an effect similar to that of a diet high in protein and with cellulose flour and hydrochloric acid added (Fig. 5-C, D). Besides inflammation, excessive amounts of protein with roughage produced severe erosion, fissuring, pin-point depressions and craters, scooped out lesions and thinning of the wall of the main stomach with the formation of diverticula in the antrum in some cases (Fig. 3-G, H and Fig. 5). The diets producing these lesions eventually led to the death of the animals by gradual starvation but the prostomach under these circumstances usually remained intact.

DUODENAL LESIONS

We already stated elsewhere (5d) that we were unable to produce duodenal ulcers in rats. Starvation and diets low in protein, as well as a diet of only white bread or with cellulose flour added, left the duodenum intact. Diets containing excessive amounts of protein often caused inflammation of the duodenum. Diets consisting of 50% or more of bran came closest to producing typical duodenal lesions in rats. That is, such diets sometimes produced erosions in small, sharply defined areas in the duodenum, 2 or 3 mm. from the pylorus. Occasionally, two eroded areas developed opposite one another, simulating "kissing" duodenal ulcers. Although duodenal ulcers did not occur in any of our rats, they were found to develop in mice (Fig. 6-B). Among 70 mice, 13 had duodenal lesions, one of these had multiple duodenal polyps, 4 had "kissing" erosions or ulcers and at least 5 had ulcers. T. P. Sun (8) previously reported that the duodenal mucosa of mice becomes denuded in 24 to 64 hours by starvation. It seems significant that both mice and humans develop duodenal ulcers and both have a gall bladder while rats do not appear to develop duodenal ulcers and also have no gall bladder. This suggests a relation between duodenal ulceration and bile flow, and bile flow may in turn depend upon liver function and protein metabolism (5d, 9).

ATTEMPT TO MAKE ULCERS CANCEROUS

After finding that ulcers could be produced easily in the prostomach of rats by starvation or protein restriction, we tried to make them chronic or cancerous. It was thought that mechanical irritation by a diet containing bran should suffice to prevent the healing of ulcers but prostomach ulcers healed in all cases where large amounts of bran were fed for a few weeks. We therefore tried to produce chronic or cancerous lesions by subjecting rats to repeated periods of relatively prolonged starvation or protein

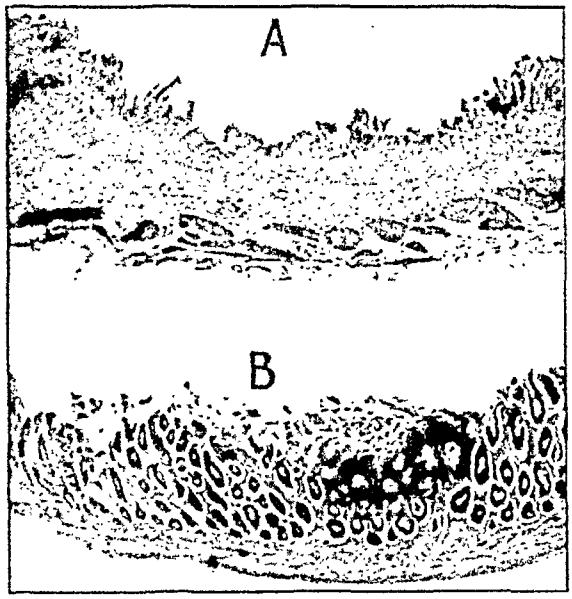


Fig. 6. Showing, A, section of ulcer in antrum of stomach indicated in Fig. 5—A. U.; and B, section of duodenal ulcer in mouse starved 36 hours after 9 days on ground washed bran plus 13% corn oil; similar lesion opposite this in duodenum.

restriction, with more or less adequate realimentation between such periods. As a result, some degree of cumulative ulceration and epithelial overgrowth was often produced. In some cases, epithelial cysts and cornified nodules developed in the ulcerated prostomach (Fig. 3-F; nodules also appeared in the stomachs shown in Fig. 1-A and Fig. 3, A). The cornified masses were due to downgrowths of the squamous epithelium in ulcers and resembled the "cancerous" changes produced by Fibiger (10) by feeding rats spiroptera or cockroaches infected by spiroptera. However, Fibiger fed his rats white bread exclusively and was able to produce the "cancerous" changes only in black-and-white rats. We also noted that cornified nodules developed most easily in black-and-white rats *and precisely when they were simply fed only white* bread (Fig. 6-A). But similar nodules also developed in white rats as a result of repeated starvation or protein restriction (Fig. 6-B). Fujimaki and other Japanese workers (11) reported the finding of "cancerous" changes in the prostomach of white rats and mice fed various diets but, like Fibiger, they failed to note any relation of such changes to protein deficiency and ulceration. As a matter of fact, none of the observed morphological changes were ever cancerous and experimental cancer from ulcer still remains to be produced.

HEALING OF ULCERS

Most ulcers produced by starvation or protein restriction healed completely when diets adequate in protein were fed but some cornified nodules and small cysts tended to remain. The healing response to a single meal of adequate food after a prolonged fast was striking. This was observed when some rats died within a few hours after they voraciously devoured a large amount of food immediately after a protracted fast. Death was probably due to increased bleeding of ulcers or other lesions and the extra tax of the excessive food intake on a feeble organism. (Humans suffer similarly—sometimes die—as a result of dietetic excesses after prolonged food restriction). In the rats, excepting for the gross lesions, the mucosa of the stomach and small intestine to within a centimeter or two of the head of the column of recently ingested food always appeared much more like normal than the part of the intestine that had not yet been reached by food. Nevertheless, the complete healing of some prostomach ulcers evidently took a little longer than their formation by our most direct method — prolonged starvation. *Otherwise a cumulative ulcerating effect* could not have occurred, as it did, when rats were intermittently starved about 4 days or more at a time and fed freely during periods of only similar length.

The value of a diet high in protein, as an aid in the healing of gastric lesions, seemed indicated by the finding of Harvey and Howes (12) that such diets help to heal experimental wounds of the stomach of rats but evidence was obtained in our study that an excessive protein intake, immediately after a period of protein restriction, often has a detrimental effect at first. Rats that had more or less free choice and spontaneously selected milk and bread as the principal food immediately after prolonged fasting seemed to fare best. However, as already indicated, prostomach ulcers frequently healed even when bran was fed. This may have been due to the protein supplied by bran (which is fairly rich in essential amino-acids), its acid-binding power or the shifting of the acid gastric juice burden from the prostomach to the main stomach and duodenum. Pregnant rats, *which generally developed* the most striking ulceration with inadequate diets, showed more or less healing shortly after casting their litters, which were always removed in these cases. This was apparently a consequence of the protein intake involved in eating the placentae. In tests on 13 rats, histidine (0.5 to 1.0 c.c. Larostidin daily per rat) did not prevent ulceration of the prostomach when a diet low in protein was used. An adequate supply of other amino-acids seems to be as important as an adequate supply of histidine. On the other hand, our results did not confirm the finding of Windwer and Matzner (13) that prostomach ulceration is increased by histidine (Larostidin).

PEPTIC ULCERATION AND PROTEIN-HUNGER

Our studies on rats and mice would seem to make it obvious that in these species there is a direct relation between peptic ulceration and protein-hunger. That is, rats and mice evidently eat a certain amount of protein at least partly *in response to peptic stimulation* or titillation and to prevent peptic irritation or ulceration. The same mechanism apparently also compels rats and mice to eat a certain amount of biologically adequate protein. Whether ulceration occurs because of a lack of sufficient acid-binding protein in the diet (or in the stomach) or because of an increase in gastric acidity following protein restriction or because of a lowered resistance to ulceration or a combination of these possibilities, a relation between peptic stimulation, irritation or ulceration and protein-hunger or amino-acid-hunger would still be indicated. In addition to this, we had evidence that an excess of protein also tends to produce gastric lesions and this suggests a mechanism which would normally limit the protein intake. These findings therefore help to ex-

plain why rats and mice tend to select a moderate and practically optimum amount and biologically adequate protein when they have free choice (14).

The difference between these species and other species is very likely only one of degree. There is no doubt that carnivores like dogs can tolerate both starvation and an excessive protein intake better than rats, mice or humans but it is not so certain that dogs or humans can tolerate protein deficiencies much better than rats or mice. Obviously, allowances must be made for differences in metabolism, length of life, etc. But Weech (15) observed ulceration in dogs fed diets low in protein. Chittenden and Underhill (16) found duodenal ulcers in dogs fed biologically poor protein. Ivy (17) noted that cachectic dogs were more likely to have gastric lesions than well nourished animals. Koschtojanz (18) found that the first phase of gastric secretion is increased in dogs by a diet without meat and Pankratjew (19) reported the perforation of a gastric ulcer in a man on a hunger strike. On the other hand, a fairly dependable mechanism normally regulating the protein intake is indicated by the fact that most humans, as well as omnivorous animals, tend to use a moderate and practically optimum amount and adequate types of protein when free choice is possible (4, 20). It seems that the question has not been whether such a mechanism exists but rather what it consists of, what its limitations are, how it becomes disorganized and how it may be controlled.

In our opinion, the failure of investigators to note the relation between protein or amino-acid deficiency and peptic stimulation, irritation or ulceration long ago is due to the neglect of a sufficient study of the factors influencing the fasting gastric secretion. This apparently began as a result of the classical work of Pavlov (21) in which he demonstrated that *the lavaged stomach of a well fed dog does not secrete gastric juice without chemical or psychic stimulation.* This dictum led many uncritical followers of Pavlov to maintain that *acid gastric juice is never secreted under any other circumstances by the normal "empty" stomach,* including that of man. Carlson (22) pointed out that there was a more or less continuous secretion of acid gastric juice in normal human subjects, as well as in some animals, and that the acid juice seemed to give rise to an appetite-like sensation in man. The relation of the continuous, basal or fasting gastric secretion to hunger was next investigated by the senior author of the present report in a study made upon himself. As a result, periodic variations in the fasting gastric secretion or contents were found to occur and to be related to the periodic changes in fasting gastric motility (3a). This finding was confirmed by Hellebrandt (23). Thus far others do not seem to have undertaken any studies on man that might confirm our observation of a relation between variations in protein intake and the fasting gastric acidity (3b) or between the fasting gastric acidity and protein-hunger (4) but the results of our studies on rats and mice seem to amply support our earlier findings on man. The evidence thus far published in support of the theory of Weiss and Aron (24) concerning the rôle of amino-acid deficiencies in gastro-duodenal ulceration does not seem to have been convincing (25) and, in any case, could hardly be directly applied to our own findings.

SUMMARY

Ulceration of the prostomach and main stomach of rats and mice and ulceration of the duodenum of mice but not of rats was found to occur as a result of starvation or diets deficient in protein or in essential amino-acids.

Ulceration thus produced is regarded as objective evidence of protein-hunger or amino-acid-hunger which has been carried to a pathologic extreme.

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The Pathogenesis of Senile Osteoporosis

Relations to Morbus Cushing and Basophilia of the Anterior Pituitary

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ERNST LYON, M.D.

JERUSALEM, PALESTINE

ACCORDING to Schmorl and Junghanns, osteoporosis is one of the most frequent changes, affecting the whole bone system. Disturbances of nutrition, changes in the internal secretion, cachectic diseases, chronic biliary fistulas, etc., were assumed to be exciting factors. "Puerperal" and "Hunger" osteoporosis are well-known and have often been described. Osteoporosis is chiefly a disease of old age.

In a series of osteoporotic pictures the changes are roentgenologically and anatomically identical. Senile osteoporosis, as well as puerperal osteomalacia, takes up a special position in a clinical sense. Senile osteoporosis develops in the whole bone system. It is neither all the bones nor always the same ones that are attacked. The processes in osteoporosis are to be observed with special distinctness in the vertebral column.

Senile osteoporosis develops when the bone apposition ceases, while decompensition is normal or increased. Changes of form and structure are to be found. In respect the form changes of the vertebral column, here only the "hour-glass" and the "fish-vertebra" shapes, the flattened and wedge-shaped vertebrae should be mentioned. The structural changes, especially in the vertebral column, are represented by diffuse porosis. The histological findings show a porotic frame of spongiosa. In contrast with the normal spongiosa, the trabeculae are scanty, thin and more perforated. The spongiosa weakened in its solidity is, in addition, brought to atrophy by the physiological pressure of expansion of the intervertebral disk, the gelatinous nucleus being intact.

As to the *bone changes themselves*, we should not think that the relations are too simple. The senile increase of bone brittleness has its origin in essence in the physico-chemical fact of aging (Schade). Under *normal conditions*, however, a decrease of the phosphates in the bone-ash can also be observed; but in a still larger amount this can be found in senile osteoporosis (Tannhauser). Etienne and Douplais found in senile osteoporosis a strongly negative lime-balance, decrease in the *Ca* content of the bones and an increase in the *Ca* content of the soft parts in opposition to the rule. In any case, this osteoporosis differs even in the chemical-analytical findings from the malacic bone diseases, such as rickets and osteomalacia.

Regarding the *symptoms of senile osteoporosis*, we can only mention here that everything that is characteristic of senile osteoporosis may also occur in other diseases. In the forefront, we find signs of senescence, pains in all possible parts of the body, conditions of weakness. In the *X-ray picture*, the chief finding is that the bones are deficient in lime. In some (not in all) cases we find a striking "decrease of resistance"; the disposition towards disease is increased, the struggle against infectious diseases rendered difficult.

Much has been written on the *pathogenesis* of senile osteoporosis. Hitherto investigators have not succeeded in clarifying the subject. Kienbock recently, again made an attempt to explain the osteoporotic diseases as "degeneracy diseases," as a dysplasia and a dystrophy of the skeleton. He assumes a strong and widely spread inferiority of the skeleton to be the exciting cause. Difficulties arose even in trying to fix the nomenclature and classification of the disease, the origin of the senile osteoporosis not being clarified. Some observers differentiate between senile osteoporosis and senile osteomalacia and acknowledge a special form of osteoporosis and a special spontaneous and another form due to hunger. It has even been believed that there are transition forms of senile osteomalacia and osteoporosis. The fact that in senile osteopathia we frequently find endocrine symptoms ought to give us the right for the designation of osteomalacia. Thus symptoms of Graves' disease, myxedema, tetany, etc., were noted, furthermore there have been noted disturbances of the parathyroid, of the pituitary gland and of the genital glands. The symptom regarded as characteristic of osteomalacia, that of the subject growing smaller, can be found in osteomalacia as well as in osteoporosis. But the therapeutic effect of phosphoric codliver-oil, of calcium and vigantol is not proof convincing enough to be employed as a dependable means of distinction in the differential-diagnostical sense. In like value can brittleness of the bones and bonebending be used as a typical sign for the one or the other form. At the moment, senile osteomalacia and senile osteoporosis are looked upon as a unity.

The calcium, as well as the mineral metabolism in general, are known to be under the regulative influence of hormones. The parathyroid gland plays a great part in the regulation of calcium metabolism. The involutional processes, too, are regulated by the endocrine apparatus, and complex disturbances of the endocrine system make the physiological process result in a clinical disease of the bone-system (Alwens). But we have not gained much by reciting these frequently-repeated statements. For we have to deal with a complex hormonal process due to a reciprocal influence of the glands and mutual advancement and inhibition by their own products. Endocrine disturbances are regularly pluriglandular. Mostly, in theoretical analytical considerations, only the chief hormonal effect is pointed out. Recent findings have been established which (also in orteoporosis) set aside general points of view and point in a certain direction. New conditions of disease of the endocrine organs having been observed in recent years, the frequent dependency of osteoporosis as a consequence of diseases of certain endocrine organs could be stated. Thus, Jamin described in a woman of postclimacteric age after the cessation of ovaric function a form of senile change, going along with hyphosis, obesity, hypertension,

cardiac weakness and hypertrychosis. Jamin indicates the similarity of this complex of symptoms to "Cushing's Disease"; plain visual observation shows these women to have full-round faces, such as are noted in the syndrome described by Cushing.

A patient of this type is described as follows: April 1, 1934. Barbara F., aged 67, 157 cm. tall, 78.5 kg. in weight, has become more corpulent during the last few years and has gone from one physician to another because of backache. Had dyspena, reddish, somewhat spongy, full- round face; broad red striae on abdomen and thighs, dilatation of the left heart, blood-pressure: 190/140 mm. Hg., tympanitic abdomen, traces of sugar in the urine. Blood: hemoglobin 90%, erythrocytes: 5,200,000, blood picture without any peculiarities. Blood sugar 190 mg. per cent. Blood calcium, 9 mg. Kyphosis of the thoracic vertebral column, first lumbar vertebra sensitive to pressure. *X-ray of the vertebral column* (lateral view) shows a pronounced lordosis of the lumbar part and kyphosis of the thoracic part, the vertebral bodies are poor in lime; only at the superior and inferior edges stripes of a somewhat increased lime content are to be found, the first lumbar vertebra is flattened and wedge-shaped, the intervertebral disk lying beneath has become smaller. In the upper part of the first lumbar vertebra a large "Knorpelknoten."

Diagnosis: adipositas, hypertension, plethora, osteoporosis, hyperglycemia, glycosuria. *Course:* Extensive improvement of the backache and loss of weight up to 5 kg., followed in two months after no therapy but roentgen-irradiation of the pituitary gland.

Differentiation between cases with constitutional obesity, hypertension and a more or less pronounced osteoporosis and an obesity of the type of Cushing (osteoporotic obesity of Askanazy) is impossible in the borderline cases. In older women obesity, hypertension and osteoporosis are no rare event. There are also benign forms of Cushing's syndrome in which some of the symptoms are absent and which remain stationary.

The picture of "pituitary basophilism" described by Cushing is known to be a syndrome in which basophile adenoma of the anterior pituitary is joined with obesity of face, neck and body, with hypertension, plethora, hypercholesterinemia, striae, osteoporosis of the skeleton (in more than 70 per cent of the cases) and sexual hypofunction. Frequently, there is a disposition towards infectious diseases manifesting in threatening outbursts. In some cases, a series of symptoms is absent; the process can proceed quickly; however, it can also remain stationary over a long period.

April, 1935: A typical case of Cushing's syndrome under my own observation, showed the following main features: A young German man, born in November 26, 1911, 8 years in school with good certificates. Afterwards he left the occupational school with very good results. From his 13th year he grew bigger. From his 19th year he has complained of becoming fatigued. From 1930 up to 1935 the faitgue and feebleness increased still more; frequent bronchitis and rheumatic affections. In his 17th year, slight dizziness; these attacks increased from year to year. He often falls down and loses consciousness for a short time. On this account, a professor of internal medicine thought this picture to be that of epilepsy and proposed to have the patient sterilized. In order to discuss this affair the man called on me (May, 1935), as I had observed in him a considerable hypertonia (210 mm. Hg.) of a permanent character in 1933.

Findings in *April, 1935:* Heavy young man, 187 cm. tall, 104.5 kg. in weight; marked obesity of body and face without participation of the extermities; the face somewhat spongy, slightly reddish-brown in color, scanty hair on the head; acrocyanosis; broad red striae of the skin of the abdomen, the shoulders, the upper arms; thoracic organs: clinically and roentgenologically without any peculiarities; blood pressure 170/110 mm. Hg., the electrocardiogram was normal; abdominal organs without any peculiarities. The blood-picture shows an increase of hemoglobin up to 115 per cent, erythrocytes: 5,320,000; in the differential blood-count there was lymphocytosis; sedimentation rate 5/14 mm. test for lues, negative; blood sugar in the serum, 111 mg. per cent; calcium content, not increased; the blood sugar tolerance test there was a rise up to 154 mg. per cent, with 150g of grape sugar; three hours later return to fasting level. The basal metabolism reduced to 9%. Protein tolerance: within 1½ hours rise to +7%. In the urine was normal as was the renal function. X-ray picture: on both the *capita humeri*, osteoporotic processes were seen, together with a slight deformity. X-ray picture of the vertebral column showed a more pronounced waist-shape of the lumbar vertebrae, the markings of the vertebral bodies being hazy; spina bifida of first sacral vertebra; X-ray of the skull showed a normal sella turcica; somewhat hazy markings of the skull bone in the upper area, this fact perhaps speaking in favor of an early osteoporosis. Genital organs normal.

Deep roentgen irradiation of the pituitary gland resulted in a loss of weight and a diminishing of the blood pressure. Then the patient gained in weight again. In the beginning of February the dizziness occurred again more frequently than usual, but only for one minute. At night the patient becomes blue from these attacks, in the day time he quickly improves. After the pituitary gland had been irradiated again more intensely, he lost 10 kg. in weight, and, at the end of February weighed 108 kg.

When comparing the disease of the woman, aged 67, with the severe disorder of this young man, the similarities become apparent. The case of the young man is—so to say—the exaggeratedly developed reflection of the benign stationary form of the post-climacteric woman. Kylin is right in saying that, in such cases, the difference is that in Cushing's syndrome the symptoms have been more worked out by nature and are therefore more striking. However, the main symptoms: special type of obesity, arterial hypertension, plethora, osteoporosis, etc., are the same. The cases reported indicate, with their like features, a relation between Cushing's hypophyseal adenoma and the obesity accompanying hypertension and osteoporosis, occurring in older women. According to Raab, adenoma of the anterior pituitary reflects in an exaggerated way the chief signs of old age; close study would perhaps be able to give an insight into the physiology of age. Kylin points out the similarity between hypertension diseases, occurring after menopause, and the symptoms of the basophile adenoma of the pituitary gland, and he considers "essential" hypertension to be the consequence of a hyperfunctional condition of the anterior pituitary due to a reduction of the inhibiting influence of the generative glands. Jores comes to the same conclusions; he found in the serum of some people, affected with hypertension, substances calling forth the same histological changes and having the same chemical qualities as the corticotrope and adrenolotrope hormone of the anterior pituitary. Berblinger, however, refuses to look upon the basophile increase in so simple a way as its the anatomical expression of the permanently increased formation and effect of vasopressin, and to ascribe the essential hypertension merely to that fact. Kraus thinks that the basophilia of the pituitary gland in Cushing's

syndrome is not the exciting cause of the disease but only a secondary change of the pituitary gland, occurring in the course of the disease. In opposition to which Berblinger looks upon the basophile adenoma, as well as the more rarely-occurring strongly diffuse basophile increase of the anterior pituitary, as a primary pathological process. However, Kraus as well as Berblinger and Rutishauser, hold that there is no doubt that there is a connection between the basophile elements of the pituitary gland and bone decomposition. In favor of this fact, he calls attention to the increase of the basophile cells at a higher age, which likewise inclines towards osteoporotic altrations, and the observation of a high degree, an unusual increase of the basophile cells of the pituitary gland in severe osteoporosis. According to Rutishauser, in those cases in which osteoporosis had been developed in a high degree, an unusual increase of the basophile cells of the pituitary body could be expected.

We regret that in most of the reports of autopsies in cases of a high degree of osteoporosis there are no observations recorded regarding the pituitary gland, *e.g.* in the case of Imhauser. We can understand that Berblinger, in an observation of a woman, aged 78, affected with Cushing's syndrome, first looked upon the porotic changes as senile ones. According to Berblinger, in this syndrome are to be found "no pronounced development of osteoclasts with lacunar resorption of the bone, but thin trabeculae of spongiosa with wide spaces filled with marrow and a reduction of the corticalis from the side of the medullary cavity." Schmorl and Junghanns in cases of osteoporosis found merely a reduction of the single trabeculae of the spongiosa as well as the bone end-plates and slight reduction in the number of trabeculae. The X-ray pictures in Cushing's syndrome and in senile osteoporosis are similar. In both the cases an increased permeability of the bones to rays is noted, the finer structure being absent. Where the latter can still be seen, the trabeculae are thin and scarce. Infractions and transverse fractures can be observed in both the pictures. The interpretation of the finer hormonal processes, originating the osteoporosis in Cushing's affection, presents great difficulties. Jamin believes in a secondary influence from the parathyroid gland. Berblinger also thinks that the effect of the parathyrotropic hormone upon the pituitary gland is credible. He also thinks it possible that there is a "Wirkstoff," produced by the basophile cells of the pituitary gland, contrary in its effect to the growth hormone of the eosinophile cells. Some very interesting observations have been made by Collip and his co-workers. He has shown that, in the case of a production of growth hormone, antihormones also are found in the anterior lobe of the pituitary. This has led him to postulate the phenomenon of "inverse responsiveness," *i.e.* balance between hormone and antihormone. The basophilia of the anterior pituitary may be due to a disturbance of this balance. Perhaps this antihormone represents the supposed parathyroid hormone. We must take into consideration these lines of thought, if we intend to consider senile osteoporosis as an effect of the increase of the basophile elements of the anterior pituitary.

Kraus thinks that basophilia by itself is not sufficient to call forth changes in the bones. But just as the basophilia plays an essential part in the pathogenesis of hypertension and in Cushing's disease, so the increase of these elements is of decisive importance for the development of senile osteoporosis. Senile osteoporosis is consequently due to an abnormal behaviour of the pituitary gland in consequence of the absence of the controlling effect of the generative glands, being in a state of involution. In future, investigations will have to deal with the question of whether (1) senile osteoporosis is merely due in part to a changed hypophyseal function and must be assumed to be partly the consequence of a correlatively influenced functional change of the other endocrine organs, or (2) senile osteoporosis may also occur without those hypophyseal changes.

Recently, it has been stated, that in adults of more advanced age, osteoporosis can also develop(it being due to an insufficient administration or utilization of vitamins A or D. People are inclined to take into consideration, in explaining the origin of all sorts of bone diseases, lack of vitamin A or D. Thus the regional prevalence of hyperparathyroidism in the great industrial districts is ascribed to the short duration of sunshine and the limited securing of vitamin D, as a consequence. Thannhauser refuses to acknowledge the malacic diseases, hunger and senile osteoporosis as a nosological unity, in spite of the conformity of their histological pictures. It is not possible to consider these osteoporotic bone diseases as similar in origin to infantile rickets. The senile osteoporosis is classed with diseases due to the withdrawal of calcium and phosphate. But important relations, existing between lack of vitamin E and basophilia of the anterior pituitary, have helped in clarifying of the pathogenesis of hunger osteoporosis (Lyon).

If one desires to exert a therapeutic influence upon senile osteoporosis, he is forced to intervene in the ring of hormonal correlations and to equalize disturbances. The anterior lobe of the pituitary gland is known to be a glandular organ highly sensitive to radium and answering promptly to irradiation. By roentgen irradiation of the pituitary gland the osteoporosis in Cushing's syndrome has also been essentially improved (Jamin). Roentgen irradiation in senile osteoporosis has already been recommended formerly (Schlesinger). It is especially in cases of senile osteoporosis accompanied by obesity, at the climacterium, in which an improvement can be expected. In mild cases and for after-treatment, the administration of vitamin E may be tried; it causes no secondary manifestations, even in prolonged administration and in high dosage. Certainly, however, an essential for the beneficial effect of vitamin E is that the involution of the generative glands has not gone too far (Guggisberg).

SUMMARY

Senile osteoporosis is due to the increase of the basophile cells of the anterior pituitary, as a result of the controlling influence of the generative glands being in a state of involution

As a therapeutic measure, roentgen irradiation of the pituitary gland and, in mild cases, vitamin E are recommended.

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Editorial

NEW KNOWLEDGE ABOUT THE FUNCTIONS OF THE SMALL BOWEL

IT is a remarkable fact and a sad one that the gastro-enterologist who struggles every day with the problems of indigestion knows practically nothing about the digestive and absorptive functions of the main organ of digestion, the small bowel. What is worse, he doesn't even realize, unless he stops to think, that it is the organ of digestion. All his training in college was given him with the thought that it is the stomach that he has to worry about and treat.

So strong is the hold of this assumption on scientific men that sometime ago, when physiologists and pharmacologists began to study the mechanism of vomiting, years had to pass before it occurred to anyone to think of what might be happening in the small bowel during the act. Similarly, even today, when a drug house prepares a medicine which is somewhat upsetting to digestion, the custom is to put it into keratin coated capsules so that it can be carried untouched through the stomach and out into the small bowel. This is done with the naive assumption that the stomach is the only digestive organ that needs to be considered. Actually every bit of physiologic evidence we have indicates that the stomach is far more resistant to irritants than is the small bowel, and much experimenting on animals and man indicates that nausea and vomiting can be induced more easily by irritation of the duodenum and upper part of the jejunum than by irritation of the stomach. The physiologist tells us moreover that one of the main functions of the stomach, for which it was specially designed, is to hold back and dilute and neutralize and feed slowly into the bowel irritant foods or substances which might, in strong concentration, injure the highly sensitive mucosa of the small bowel.

No, gastro-enterologists must gradually come to see and to realize at all times that the real organ of digestion is the small bowel. There is practically no absorption of food or water or even crystalloids from the stomach. In addition to holding back solid and irritating substances, warming them to body temperature, and softening and partly digesting them, it feeds the chyme gradually and as needed into the bowel. It is the small bowel that does the final digesting and all of the absorbing.

There is no doubt but that much of the dissatisfaction that any thoughtful gastro-enterologist must feel with his work today is due largely to his almost complete ignorance of the functions of the small bowel. What is more, with patients it is almost impossible for him to learn much of what is going on in this part of the digestive tract. He can pass a tube into the stomach to remove contents for analysis, and he can study the inside of this organ with the roentgen rays or with the new flexible gastroscope. Similarly, he can look into the inside of the colon and study the folds of the mucosa with the double contrast barium meal or with the sigmoidoscope. But, as yet, he cannot learn much about the central portion of the small bowel. All he can do is to get some idea of the normality or abnormality of peristalsis and of mucosal patterns at its two ends; in the duodenum and first portion of the jejunum and in the last segment of the ileum.

It is doubtless because of this handicap that in four out of five cases of diarrhea the physician is unable to find a definite cause. Seeing that in all of these puzzling cases the mucosa of the colon appears to be perfectly normal, the probability is, I think, that the disturbance of function is in the small bowel where we cannot as yet get at it very well.

Until last year anyone who turned to the literature for information as to the laws underlying the absorptive processes of the small bowel would have found very little, and that little scattered through highly technical journals. Today at last we can turn to one well-written monograph, a monument to the industry and ability of Fritz Verzár of Basel. To him should go thanks and appreciation from all of us, physiologists and clinicians, who are interested in digestion. The book should be in the library of every man who practices gastro-enterology, and it should be read and reread. For years Verzár and his pupils have been studying the intestinal mucosa and the ways in which it absorbs and digests, and here we have a good résumé of their findings, together with a fine review of the literature. I hope in a later issue of this Journal to give some idea of the riches that are to be found within the covers of this little volume.

Other excellent work has been done in this country by Wells, Cori and others, using animals, and now Grier Miller, Osler Abbott, Karr and others in Philadelphia are studying the motor and secretory and absorptive functions of the small bowel in man with the help of special tubes which are passed through the mouth far down into the small bowel. These studies are most promising, and should some day give the practicing physician some hint as to what is going wrong in the bowel of his patients with now puzzling syndromes. Finally, when we have some idea of what is going wrong, we will have some chance of doing something that will restore conditions to normal.

Walter C. Alvarez, Rochester, Minn.

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Book Reviews

Traitement Chirurgical Du Cancer Du Colon Pelvien. By Pierre Bertrand and E. Corajod. Masson et Cie., Paris.

PROFESSOR Louis Tixier whose operation for cancer of the pelvic colon is well-known and described in the text, states in a preface that, nowadays, with rapidly improving technique, the mortality is on the decrease and one may often count on a definite, radical cure. His pessimism with regard to surgical cure of gastric cancer is in contrast to his hopefulness when the disease is situated in the rectum or colon. The report itself concerns an intimate follow up of 155 cases. Constipation and (or) diarrhea are the chief early symptoms, along with pain in the lower left quadrant and vague indigestion leading to suspicion of gastric trouble. Then follow symptoms associated with gradual stenosis—with bloody and mucoid stools, pain, irritable bladder. The evolution is very slow—occlusion, suppuration, fistula formation, perforation, general metastases. Precise location of the obstruction by X-ray studies is essential: a preliminary film without barium is frequently of value in showing colonic distention with gas. The barium meal ought not to be used after obstruction is complete. The opaque enema is the method of choice, and the study of mucosal relief patterns has proved helpful. Treatment is essentially that of radical removal with reestablishment of continuity of the gut. Variations depend upon exteriorization in contrast to intra-abdominal operation; and also the formation of an artificial anus. Hartmann's operation is intra-abdominal colectomy with anus formation. Tixier's operation in three stages is fully described. Encouraging results are tabulated from a prolonged follow up of cases. A note of warning is given with regard to the possibility of luetic lesions of the sigmoid resembling cancer.

Beaumont S. Cornell, Fort Wayne, Ind.

The Little Things in Life; the Vitamins, Hormones, and Other Minute Essentials for Health. By Barnett Sure, Ph.D., Professor of Agricultural Chemistry in the University of Arkansas. 340 pages; published 1937 by D. Appleton-Century Company, New York. Price $2.50.

THE object of this book is to bring to the attention of the layman present day scientific knowledge regarding vitamins, inorganic salts and hormones. The author is on familiar ground when he deals with vitamins, particularly the "B" group, but when he discusses the ductless glands and their relation to nutrition he shows less familiarity with the subject. This book contains less discussion of rats and guinea pigs, and more of the application of the value of accessory food substances to human nutrition than most books on the same subject for laymen. As would be expected the two chapters dealing with vitamins in infant nutrition and during pregnancy and lactation are the best in the book.

The Little Things in Life are the vitamins, mineral elements and ductless glands. These have been discussed by the author in a sound, sane manner. This book can be recommended to your intelligent patients. The gastro-enterologist could afford to read Barnett Sure's book to get the view point of such an experienced biochemist in the field of deficiency diseases.

Lloyd Arnold, Chicago.

Abstracts

FALSI, ERNEST CALROLL.

The Use of Anthelmintics. J. A. M. A., Vol. 108, p. 256, Jan. 30, 1937

The anthelmintic drugs are those used to remove parasitic worms from the body of the host. In human infections the ones used are primarily drugs and dyes which act to narcotize, kill, and at times digest the worms. An ideal one is lethal to the parasite well within the limit of tolerance of the patient. Before using an anthelmintic it is well to know the species of parasite involved, the location and number in the body, the actual or potential damage produced by the parasite, the dosage of the indicated drug in adults and children, and the method of determining the efficacy of the anthelmintic following its administration.

Betanaphthol, thymol, oil of chenopodium, carbon tetrachloride, tetrachlorethylene, santonin, hexylresorcinol, ficin, and gentian violet are the most important chemotherapeutics useful in removing intestinal nematodes. Tetrachlorethylene is probably the safest efficient drug for hookworm infection, and hexylresorcinol for ascariasis and seatworm infection. Gentian violet is specific for strongyloidosis infection. Ficin is probably the best for trichocephalis infection, but is not yet available to the profession. Oil of chenopodium is very toxic and is contraindicated in many cases, although it is very potent for both hookworm and ascariasis. Carbon tetrachloride also is very toxic, but also is very effective in the treatment of hookworm and tapeworm infection.

Oleoresin of aspidium and pelletierine tannate are both very toxic, but are used in removing tapeworm. Antimony and potassium tartrate is the drug of choice in blood fluke infection. Emetine hydrochloride has not been found to be of much value except in fascioliasis. Creeping eruption is best treated by the local application of ethyl chloride.

Francis D. Murphy, Milwaukee.

BROWN, CLARENCE F. G. AND DOLKART, RALPH E.

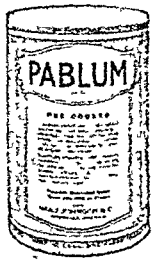
Keto-cholanic Acids in the Medical Management of Low Grade Gall Bladder Disease. J. A. M. A., Vol. 108, pp. 453-461, Feb. 6, 1937.

Gall bladder disease is a well recognized cause of upper abdominal distress. The therapy of this condition is highly controversial. Some men believe that the only therapeutic measure is removal, while others believe that removal is indicated only when stones are present. The accepted medical management at the present time consists of a low fat diet, duodenal drainage, cathartics and biliary antiseptics.

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should be used if pus or other secretions are present. If erosions are present they should be irrigated with weak silver solutions. Milk should be avoided in the atrophic form. Hydrochloric acid may relieve some of the distress. Parenteral liver should be tried in all atrophic forms.

Francis D. Murphy, Milwaukee.

STUCK, I. E., DEUTSCH, H., REED, C. I. AND STRUCK, H. C.

"Further Studies on Intoxication with Vitamin D." Ann. Int. Med., X, 951, Jan., 1937.

The work reported by these authors on Vitamin D was built around the following hypotheses.

(1) Proper vitaminosis D may produce symptoms of hyperparathyroidism.

(2) The therapeutic use of Vitamin D is rational only in conditions of known deficiency.

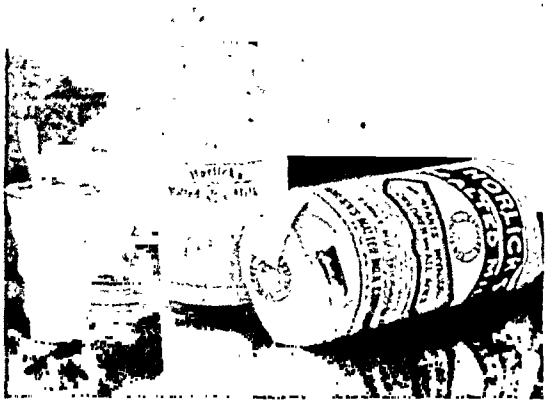
(3) Animals experimentally treated with Vitamin D concentrates have shown extensive calcium deposits in various tissues and other pathological changes have been found.

Their work covered observations on dogs, supplemented by studies on human beings.

In their experimental work on dogs they found that the changes which occurred as the result of the toxic effects of Vitamin D consisted of a cellular injury which took precedence in occurrence and that this was followed by calcium deposition at the site of the cellular injury. Extensive damage to renal structures was noted, while medial thickening in arteries was observed in but four of the 64 dogs studied. Loss of weight was a rather common result and this they thought was due to impoverishment of fat depots. Premortal coma was described as one of the characteristic features of fatal hypervitaminosis D. This condition was usually preceded by partial paralysis, slow shallow respiration, fine, thready, rapid pulse, salivation and frequently by psychic changes of such nature that a previously friendly dog would become unmanageable or even vicious. The objective symptoms of toxicity noted are listed as weakness and lassitude, anorexia, polydipsia, polyuria, diarrhea and psychic disturbances. The bloody feces observed was explained on the basis of petechial hemorrhages found in both the stomach and the intestines at autopsy.

As a matter of dosage they noted that dogs received 20,000 units or less per kilogram of body weight showed no evidences of cell injury and only an insignificant weight loss, with very little toxic manifestations. The observations on these dosages covered a period up to 153 days. Attention is invited to the fact that diet is a very important factor in conditioning toxicity of animals. They feel that there is no causal relationship between what is termed hypercalcemia and toxicity, and object to the use of these terms interchangeably by authors.

In their observations on human subjects attention is invited to what appears to be enormous doses of Vitamin D that have been administered to human beings, but they claim that when consideration is given to the weight-dosage relationship that few of the human subjects reported have ever received doses comparable to the large doses tolerated by their dogs in their series of observation. The routine dose which they gave to human beings ranged up to 200,000 units daily for periods covering from seven days to two years. This represents approximately 4,000 units per kilogram per day. The shortest period of administration that resulted in intoxication in their group of human beings ran from 3 to 5,000 units per kilogram per day was 87 days. In the group that were on a dosage of from 6 to 7,000 units per kilogram per day the shortest period for development of toxicity was



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66 days. The symptoms that they list as characteristic of hypervitaminosis D in human subjects are dependent first upon cellular degeneration that occurs most commonly in the kidney, with a concurrent loss of weight, and second, to a deposition of calcium which occurs at the site of all cell injury, and third, up to advanced stages of toxocity they concluded that these processes were reparable if Vitamin D administration be discontinued. Calcium appears to be excreted by the urine when removed from tissues during recovery, and it may be concluded that repair is not complete in any patient until the urine calcium excretion becomes normal. The source of the initial increase in calcium in the urine has not been definitely determined, but it is thought to come from the trabeculae of the bones. Concerning the factor of age they state that older subjects are usually less readily intoxicated, but recover less readily when intoxication does occur than in the younger persons. They have found on record only two instances of death in human subjects certainly due to hypervitaminosis D. As a contraindication to the use of Vitamin D they suggest that kidney dysfunction should constitute an absolute contraindication, for the present, at least. They also believe that hyperthyroidism accentuates the tendency toward pathological effect.

The article concludes with the following summary and conclusions:

1. Observations on 61 dogs and 773 human subjects receiving massive doses of Vitamin D have been made and data recorded as to the dose per unit of body weight and on the nature of the process of intoxication.

2. Both human subjects and dogs generally survive the administration of 20,000 units per kilogram per day for indefinite periods without intoxication.

3. Hypervitaminosis D first produces cell injury followed by calcium deposition. This process is reversible and reparable if administration is discontinued promptly.

4. Intoxication for short periods does not result in any permanent injury that can be recognized by the methods employed in this investigation.

Virgil E. Simpson, Louisville.

GRAHAM, ROSCOE R.

Diverticulitis of the Sigmoid Colon. Can. Med. Asso. Jour., 36:1, 1-7, Jan., 1937.

Many cases of colon disturbance are labeled and treated as "colitis" without proper examination and study. Most of such cases are functional but occasionally there is an organic lesion responsible, especially carcinoma or diverticulitis. The reason for seeking relief is one or both of the following reasons: a change in the rate of flow of the content (diarrhea or constipation) or a change in character of the content (increase or decrease of fluid, presence of blood, mucus, or pus).

Diverticulosis which must precede diverticulitis, is present without symptoms in about 5% of persons subjected to X-ray examination of the colon for any cause. Diverticulitis develops in approximately 12% to 15% of cases of diverticulosis. The frequency of diverticulosis is about 12 in a thousand; that of diverticulitis is one in a thousand. Diverticulitis rarely occurs under 35 years of age. This study of 41 cases covers a group which had progressed to a point requiring surgical consultation.

Acute diverticulitis is divided into *simple, non perforating, and perforated.* Chronic diverticulitis is divided into *non-perforating with adhesions and obstruction and slowly perforating with abscess about the sigmoid, in the mesentery, or into adjacent viscera.* Twenty-five per cent of the patients in this study underwent emergency operation for acute perforation. Diagnosis in the acute group is difficult. No mass

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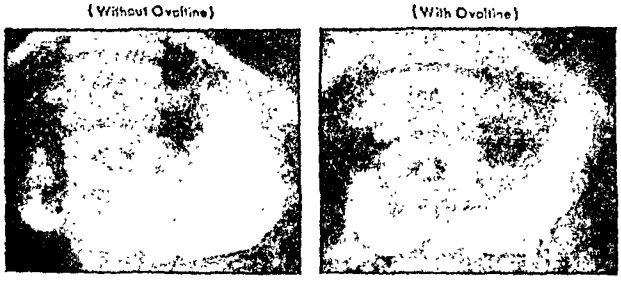
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The two x-ray reproductions show the stomach two hours after a starch meal was taken, with and without Ovaltine. The average decrease in gastric contents due to Ovaltine was 20%.

was palpable in the acute cases. "Pain in the lower abdomen—radiating to the rectum and temporarily relieved by the passage of flatus or stool, is a very significant symptom." The results from general treatment with intravenous fluids, heat locally, and sedation are justified even though operation is delayed several hours. Operation consists of exposure of the perforation, the placing of a rubber tube to the site, and walling off the surrounding area with gauze saturated with liquid paraffin containing BIPP. In obstruction requiring decompression a cecostomy is preferred to a colostomy because it is *simple, effective, easy to close*, and it acts as a safety valve if resection is necessary. Cecostomy is done by attaching the bowel to the skin by interrupted sutures.

Most cases of chronic diverticulitis are characterized by "recurring vague abdominal distress with definite periods of acute illness" in patients over 40 years of age. Symptoms commonly consist of constipation, fever, and acute pain. Less often there is bleeding, tenesmus, obstruction, lower abdominal mass or a tender mass palpable rectally. X-ray is of distinct help in many but not all cases. The cases treated were practically all surgical and therefore an opinion concerning early treatment is of no value. Based on the few nonsurgical cases, however, treatment would include prolonged bed rest and dietetic control with periodic examination over a year or two provided *response is satisfactory*. Resection in the cases not responding to the above treatment would save invalidism, economic loss of time, and the possibility of erroneous diagnosis especially in carcinoma of which there were seven cases in this group.

The presence of a mass is not an indication for emergency treatment. Nor should a patient with a left colon mass be diagnosed carcinoma until diverticulitis has been excluded etiologically. There were 13 diagnostic errors in this group of 44. Five cases diagnosed diverticulitis proved to be carcinoma. Differentiation of inflammatory and neoplastic lesions of the colon may be very difficult or impossible or the two may coexist.

Wayne W. Flora, Chicago.

KANTOR, J. L. AND COOPER, L. F.

"Dietetic Treatment of Constipation with Special Reference to Food Fiber." Ann. Int. Med., X, 965, Jan., 1937.

The authors pay their respects to the domination in medical literature of advertised artificial bulk producers in the treatment of constipation during recent years. Listed among these bulk producers is mineral oil, agar, bassorin, psyllium seed, cellulose and bran, and they call attention to the fact that these substances cannot be employed indefinitely without the possibility of interference with nutrition. They then make a plea for a refocusing of attention on diet by the medical profession in the treatment of constipation. Acknowledging the work of Rose and Cowgill and their associates, the authors stress the fundamental physiological fact of the quantitative relation between the amount of crude fiber ingested and the resultant laxative effect. They accept a daily intake of from 90 to 100 mgms. of fiber per kilogram of body weight as being sufficient for an adequate laxation. Attention is also invited to the dearth of helpful data to be found in American books on diet. For even approximate estimations of the quantitative employment of diet in the treatment of constipation the reader must go back as far as 1921, when von Noorden wrote concerning his advocacy of the use of a bulky diet for constipation. In their list of research work the authors confine their observations to fruits and



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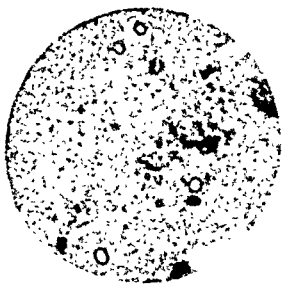
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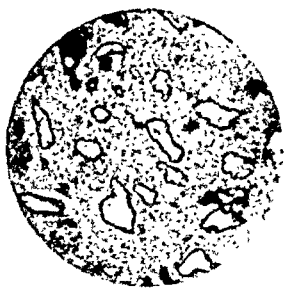


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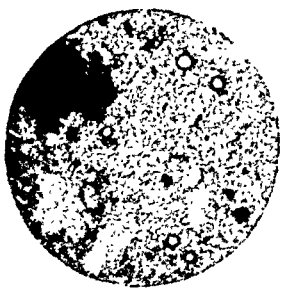


Human feces after ingestion of mineral oil. Note the large patches of free oil.

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tirely, and of this group of foods to only three representatives, prunes, apples and bananas. They found the fiber content of prunes to be 1.9 per cent, of apples 1.4 per cent and bananas 0.6 per cent respectively.

Their experimental work appears to have been well controlled and consisted of a preliminary period when the subjects on whom the observations were made were allowed what they desired. The diet on which they were subsisting was submitted to a determination of fiber content, the weight of the patient was kept and the individual laxative frequency recorded. As a result of their experimental work it was found that prunes had a laxation effect of 7.7 and a colon emptying time of 91 hours. Bananas had a laxation effect of 6.8 and a colon emptying time of 98 hours, while apples had a laxation effect of 6.1 and a colon emptying time of 115 hours. Calling attention to the fact, however, that the number of stools was not an accurate guide to the laxative effect, the following additional criteria was set up. Prunes gave the best laxative effect in five subjects, apples in three and bananas in one. Considerable variation in the personal preference on the part of the experimental subject was noted. The most constipated individual in the group rated apples first, bananas second and prunes last. This rating was made on a basis of subjective impression.

In discussing the clinical applications of some studies on diet for the relief of constipation the standard of Cowgill of 100 mgms. of fiber per kilogram of body weight was accepted, and then they insisted that in planning a diet for a constipated person the same precision with regard to the fiber content should be observed as one would exercise in prescribing a diet for diabetes or obesity. Tables were given listing foods showing the fiber content. Their observations led to the conclusion that the addition of fruits to the diet of a constipated person in the amount of 33 mgms. of fiber per kilogram of body weight added to an average diet containing approximately 66 mgms. per kilogram of fiber from other sources should relieve constipation in most of the simpler cases.

The authors give the following summary of their work.

1. An adequate fiber intake is important in the dietetic treatment of constipation. Fiber is supplied by three classes of foodstuffs—fruits, vegetables and cereals.

2. The relative laxative value of typical fruits was studied in human subjects on a fiber-equivalent basis. Previous work showing that the laxative effect of a diet depends largely on its fiber content was confirmed and the value of such typical fruits was demonstrated. Although prunes were found to be generally more laxative than apples or bananas, yet each of the latter proved more effective in individual cases. There is reason to believe that bananas are of special value in constipation associated with colonic instability.

3. Tables are furnished showing the fiber content of the common fruits, vegetables and cereals, in per cent by weight and in amount per portion.

4. In the selection of fibrous foods only bland articles should be used at the beginning of treatment because rough foodstuffs may provoke bowel irritation with resulting spasm and increase in constipation.

5. For the relief of many if not most cases of simple constipation ordinary servings of fruit should be taken three times daily, preferably as desserts. The daily use of approximately 2 grams of fruit fiber in addition to the average diet containing four vegetables

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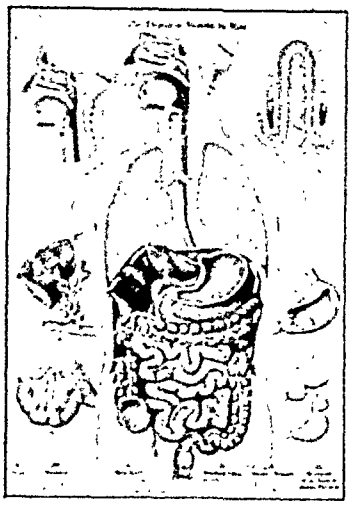
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Virgil E. Simpson, Louisville.

JUDIN, S. S.

Partial Gastrectomy in Acute Perforated Peptic Ulcer. Observation on Diagnosis and Treatment of 426 New Cases. S. G. O., Vol. 64, No. 1, pp. 63-68.

The authors present in detail a case of pancreatic fistula which developed in an 18 year old male who was kicked in the abdomen while playing football. On the day following the accident the patient complained of abdominal pain with nausea and vomiting; his abdomen was explored and a drain inserted into a hemorrhagic area in the gastrocolic omentum. The amount of fluid which drained from the pancreas varied from 532 to 663 cubic centimeters daily. The quantity varied with dietary regulations and alkaline medication. The physical and most of the chemical characteristics of the fluid are given in the article.

After a period of time during which conservative measures were tried and failed to stop the drainage from the fistula, operation was decided upon. The fistula was excised from the abdominal wall and inserted into the jejunum. Recovery was uneventful.

A review of the literature, five figures, and bibliography accompany the article.

N. M. Percy, Chicago.

LAHEY, F. H. AND LINN, R.

Cure of Pancreatic Fistula by Pancreato-jejunostomy. S. G. O., Vol. 64, No. 1, pp. 79-88, Jan., 1937.

The author describes an oblique upper right rectus muscle splitting type of incision for the suture of acute perforations of peptic ulcer. Its advantages are that it is short, easy to make, little bleeding is encountered, little packing off is required, and the liver edge helps prevent herniation of the viscera if the wound separates. This wound may be extended to permit operative procedures on the gall bladder and may be closed readily if a low abdominal incision must be made.

Five figures accompanying the article show the technique in detail.

N. M. Percy, Chicago.

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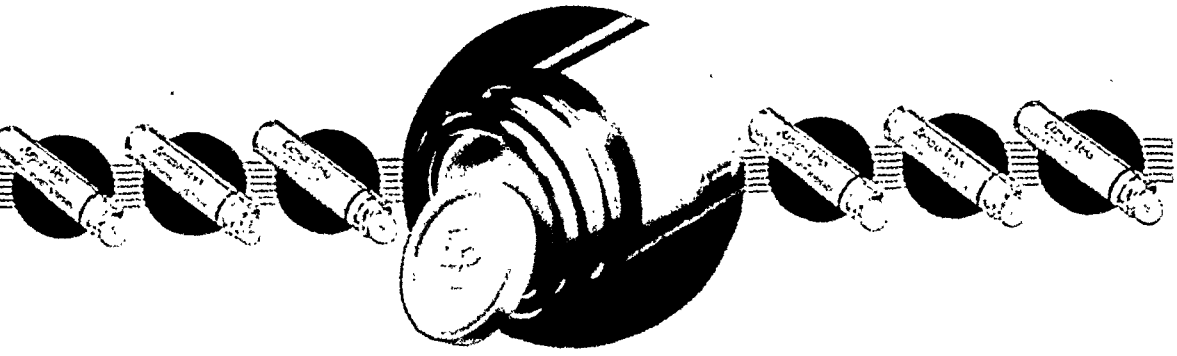
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The following abstracts are reprinted by permission from "The Borden Digest," New York, N. Y.

Calcium Requirements in Man. Edit. Brit. M. J., p. 869, April 24, 1937.

In reviewing and commenting upon a recent survey of the calcium requirements of man by Dr. I. Leitch, the *Journal* points out that this authority calculates the daily maintenance requirement of adults at 0.55 gram, whereas Sherman has put it at 0.45. Many diets in America and England do not, however, reach even this lower figure of calcium intake. During adolescence, the need for calcium is especially high, increasing up to 2 grams daily between the ages of 15 and 16 years. Assuming that milk provides two-thirds of the calcium, children of this age need two pints of milk a day.

There is evidence to show that breast milk is often qualitatively and quantitatively inadequate as a source of calcium for the infant. To maintain the optimum of 10 grams of this mineral per kilogram of body weight, the intake must be 0.2 gram at one month and 0.52 gram at 6 months, but many nursing mothers do not provide this amount. Although cow's milk contains nearly four times as much calcium as breast milk, its buffering power is greater, but this can be reduced by treating the milk with acid. One of the functions of vitamin D seems also to be to lower the pH of the intestinal contents and hence increase the absorption of calcium. There is, however, a paucity of knowledge of the processes of absorption from the intestine. Another urgent need is to ascertain whether the calcium content of breast milk can be affected by the mother's diet.

Calcium Therapy in Dentistry. Edit. J. Am. Med. Ass'n., 108:1655, May 8, 1937.

Conclusions of the Council on Dental Therapeutics of the American Dental Association regarding the use of calcium in human nutrition and in the control of dental caries are summarized as follows:—

1. All the calcium and phosphorus requirements for average needs, including pregnancy and growth, may be suitably obtained by means of an adequate diet containing not only calcium and phosphorus compounds but also other necessary factors, such as caloric, protein and other mineral and vitamin requirements.

2. There is no carefully controlled evidence that the addition of calcium and phosphorus compounds, whether inorganic or organic, promote retention of these elements and hence freedom from dental diseases, except in known cases of deficiency. Where this occurs, milk serves as an excellent source of calcium and phosphorus in a readily assimilable form.

3. There is no evidence that the ingestion of combinations of calcium and phosphorus in addition to diets adequate in these elements promotes the development of sound teeth in the human fetus. The calcification of the teeth is a postnatal event.

Foods containing vitamin D are, however, of value in exerting a favorable influence on the absorption and subsequent deposition of calcium and phosphorus in the bones and teeth, and are an aid in the prophylaxis of dental caries.

SMITH, E. E. AND FRIED, R. I.

A Clinical Study of the Apple Diet in the Treatment of Diarrhea in Infants. J. Pediat., 10:395, April, 1937.

Although there have been many reports of successful treatment of infantile diarrhea with an apple diet, the authors were unable to find any appreciable difference in the results obtained by this means or by other types of therapy. Out of 90 cases studied, 28 were put on the apple diet, and 12 on a starvation treatment followed by protein milk. The apple diet was of no value in the treatment of dysentery, and was no better for mild and severe types of diarrhea than any other type of treatment. The care of diarrhea, the authors contend, depends on rest for the gastro-intestinal tract, parenteral fluids, supportive measures, and maintenance of the mineral balance.

BRAILEY, A. G.

Treatment of Constipation. N. E. J. M., 216:697, April 22, 1937.

Ninety-eight of 100 consecutive private patients who gave constipation as the major complaint were cured by means of adherence to the following regular schedule:—

1. Sleep—a regular time for rising and, insofar as is practical, for going to bed.

2. Meals—no eating between meals (no unusual amount of roughage.)

3. Fluids—at least 8 full table glasses daily (milk, fruit juice, water, etc.)

4. Exercise—at least 30 minutes daily (strenuous enough for some breathlessness and palpable perspiration.)

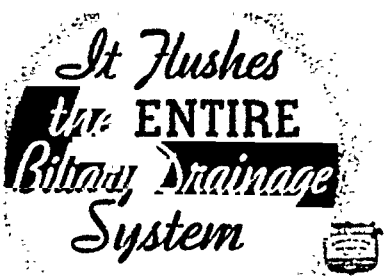
5. Toilet visit—stay 15 minutes, if necessary, without straining; if possible, ignore calls to stool at any other time; no laxative or oil is allowed, but, if 3 days elapse without any sort of stool, take a small, warm water enema at the end of the usual toilet visit on the third day.

An interval of 3 days without a stool has seldom occurred, says the author, and more than one enema has been very rarely required.

LEITCH, H. AND EDMONTON, E. E.

The Vitamin G Content of Some Foods. J. Nutr., 13:525, May 10, 1937.

The flavin, or vitamin G, content of various foods was determined in a series of tests by the Bourquin-Sherman and Murrill methods. The results showed that dried



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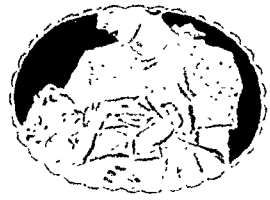
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brewer's yeast had from 20 to 21 units per gram, dried whole milk 5.3 units, cottonseed meal 2.9 units, and soy beans 2.1 units per gram. Although the milk came from a pellagrous region in South Carolina, it is apparently as potent in flavin as that from other localities. These results are comparable with those of other investigators, whose reports are cited and discussed.

The authors point out that flavin is a definite growth-promoting substance, is concerned in the maintenance of a normal skin condition, and plays a part in food utilization and stimulation of the appetite, but that recent investigations have indicated that flavin is not effective in the prevention or treatment of human pellagra. This disease yields, however, to another nutritional factor, apparently a part of the vitamin B complex, although not vitamin B_6. What was hitherto called vitamin G is now known to consist of at least the two factors, flavin and vitamin B_6.

PHILPOTT, N. W. AND BARRETT, C. V.

The Freezing of Human Milk as a Means of Preservation. Can. Med. Ass'n. J., 36:505, May, 1937.

Endeavors to reduce the mortality of premature babies, as undertaken by the Royal Victoria Montreal Maternity, consist primarily of: (1) meticulous cave-room care; (2) intelligent nursing and medical treatment; (3) adequate and proper feedings.

Since breast milk is essential for prematures, such milk is collected from healthy mothers, pooled and boiled, and the surplus is frozen and stored. The human milk is preserved by the quick freezing method with dry ice, and kept in a special refrigerator at a temperature of 10 degrees below zero. When needed, the milk is thawed. There is very little change in its composition, and there is a definite reduction in its bacterial content while frozen.

As a result of the various procedures used, there has been a gratifying reduction in the mortality of premature babies at this hospital.

(ED. NOTE: A reprint of a popular article in the May, 1937, issue of *Good Housekeeping*, which describes the quick freezing process for breast milk as developed at the Directory for Mother's Milk in Boston, will be sent on request.)

Further Advances in the Milk Industry. Edit. N. E. J. M., 216:802, May 6, 1937.

Special advantages of certified milk are outlined in this editorial, which calls attention to the fact that standards for this product are more rigid than for all other grades of milk, although practically all milks sold in Boston now exceed their standards by wide margins.

The allowable bacteria count for certified milk is only 10,000 per c.c., and when pasteurized, only 500 per c.c. All cattle are tested at least twice yearly for tuberculosis, and for the presence of *Brucella abortus*. The maximum allowable age of certified milk before pasteurization is only 24 hours, and this grade of milk must be delivered within 30 hours. It is, therefore, the freshest milk supply available.

Employees on certified milk farms are subject to medical examinations at least weekly, and cattle are examined by veterinarians at least monthly.

Pasteurization of all but a proportion of the certified milk, says this editorial, puts the final seal of safety on this important part of our food supply.

Pasteurization. Edit. N. Y. Med. Week, p. 4, May 1, 1937.

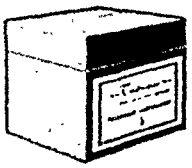
The quasi-medical article entitled "Is Milk Cancer's Ally?" in the March issue of *Current* shows so little knowledge of either milk or cancer, says this editorial, that it is very dangerous to feed. More people than should be are influenced by this sort of pseudo-scientific [illegible] are unable to evaluate the quoted results and



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frequently accept printed allegations that have no valid foundation.

"An article which without scientific evidence undermines public confidence in a basic food like milk," continues the editorial, "has no place in a reputable publication." The editors of this magazine, in their effort to be "advanced" have leaned so far forward that they have somersaulted to a bad fall. The intelligent reading public can have no respect for a publication which lags so far behind the scientific times as to accept uncritically an unverified theory linking cancer to milk.

(ED. NOTE: The May, 1937, issue of *Coronet* makes partial amends by printing an article by Dr. Clarence Cook Little, in which it is stated that there is no evidence to show that diet plays any part in cancer, and that milk certainly can not be incriminated in malignant growths.)

More Medical Misinformation From Consumers' Research. Edit. J. Am. Med. Ass'n., 108:1718, May 15, 1937.

An article on diet and common colds in *Consumers' Digest*, a more or less popular magazine issued by Consumers' Research, is vigorously condemned in this editorial. The alleged cold-preventing diet recommended in this unscientific journal would consist of adequate protein with a minimum of carbohydrate, using liberal portions of lean meat, poultry, fish, cheese, eggs, and other animal products, and restricting intake of potatoes, corn, beans, cereal, pastry, candy, syrup, soft drinks, ice cream, sherbet, alcoholic liquors, sweet fruits and "—of all things—fruit juices."

"Again, apparently without adequate consultation with medical authority, and this time even without adequate survey of recently available evidence," declares this editorial, "Consumers' Research presumes to dispense bad medical advice to its perhaps too trusting readers."

Is Pasteurization Harmful? Edit. Lancet, 232:1173, May 5, 1937.

Studies undertaken at the Rowett Institute on behalf of the Milk Nutrition Committee, of which Lord Astor is chairman, show that the changes in milk caused by pasteurization are of no consequence. There is no change in the nutritional availability of the calcium and phosphorus, no alteration in the biological value and true digestibility of the nitrogen, and no damage to vitamin A or its precursor, carotene. There is some loss in vitamin B_1, and about 20 per cent of the vitamin C disappears if the milk has been exposed to light before heating.

The results, says the editorial, "already show that milk suffers no damage by pasteurization that is important, compared with the risks of drinking it raw."

FRANDSEN, J. H.

Some Milk Superstitions. J. Home Econ., 29:243, April, 1937.

Various popular misconceptions concerning milk are corrected by the author, who gives scientific facts to prove that:—

a. Acid fruits and milk may be consumed together, with a resulting increase in digestibility.

b. Fish and milk are in no way incompatible.

c. Milk need not be sipped, but should be drunk naturally and liberally for best curd formation in the stomach.

d. Milk is a negligible source of digestive troubles.

e. Milk is not in itself a fattening food.

f. There are no physiological reasons why milk and meat should not be eaten together.

g. Milk is not merely a food for infants but is a well balanced diet for adults.

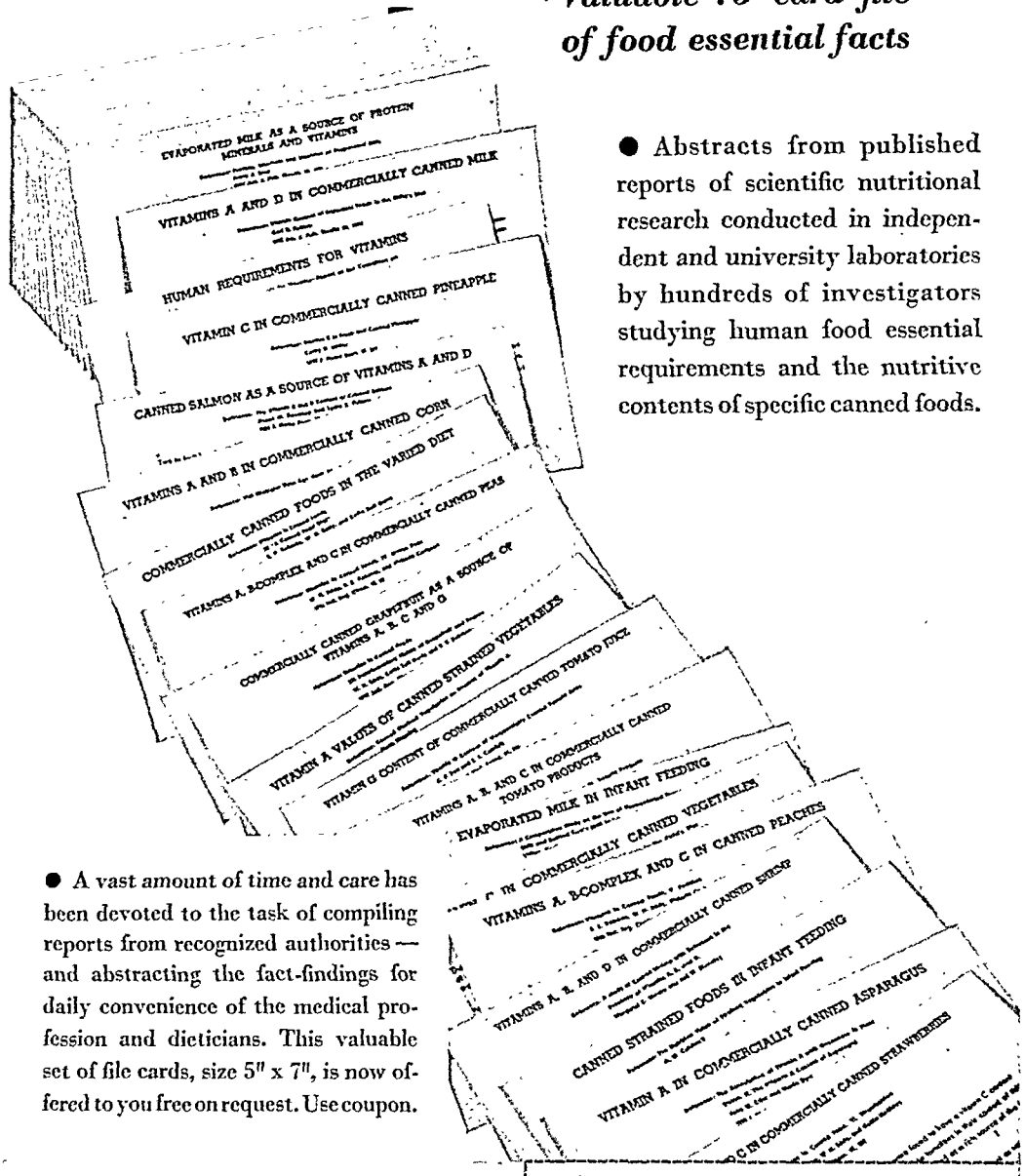
h. Milk has more solid food than most vegetables, and its bulk is not disadvantageous.

i. Milk is not constipating in a normal balanced diet.

j. An occasional exception to these facts in diseased conditions is of incidental importance.

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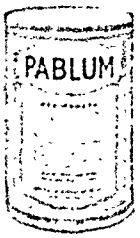
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Iron	0.03	0.0038	0.0008	0.0009	0.00024	0.003
Phosphorus	0.620	0.392	0.125	0.093	0.093	0.180
Copper	0.0013	0.0005	0.00017	0.00034	0.000015	0.00023
Vitamin B (B_1)	+ + +	+ +	— to +	+	+ +	+ to + +
Vitamin G	+ + +	+	— to +	+	+ + +	+ + +
Moisture	7.0	8.0	10.9	35.3	87.0	73.7
Protein	15.0	15.2	11.0	9.2	3.3	13.4
Fat	3.0	7.3	1.4	1.3	4.0	10.5
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Calories per oz.	106	110	103	74	20	42
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The Role of the Liver as the Commissariat of the Body*

By

FRANK C. MANN, M.D.†
ROCHESTER, MINNESOTA

IN pioneer days the head of the household was called the provider of the family. It was his duty to supply the fundamental necessities for sustaining life. The most important of these necessities and usually the most difficult to secure was food. It is in this sense that I wish to present the major functions and activities of the liver as the commissariat of the body. With such a view in mind, I have attempted to assemble and correlate what appear to be the more significant known facts concerning hepatic activity in maintaining the food supply to the body tissues and to present some of the major problems of metabolism as they relate to the functions of the liver. I realize that only a small part of my ambitious concept can be attained because of the many and intricate mechanisms involved, the inadequacy of exact knowledge concerning many of them, and the large amount of undigestible evidence presented on the subject. These facts in themselves are significant because they emphasize the importance of the liver and the need for future researches.

Food is a constant necessity for living protoplasm. It is needed for growth and repair of living tissues and for energy to produce the heat and mechanical activity of the living organism. The unicellular organism has the capacity to metabolize food in all important details, as digestion, absorption and utilization within itself, and such processes constitute a large portion of its activities. In the multicellular organism, a division of the activities related to food and its utilization becomes essential and cellular specialization necessarily develops. Higher organisms do not obtain their food continuously, but their tissues are constantly in need of foodstuff. To supply a constant stream of such material which can be quickly transformed into energy is the major function of the liver and the one which I wish to emphasize.

SOME GENERAL PHYSIOLOGIC REACTIONS OF THE LIVER

The liver has very many important general reactions; the most pertinent in relation to this subject is the rapidity and multiplicity of its activities. The multiplicity of hepatic activities in relation to metabolism need hardly be emphasized, as the capacity of the organ in this respect is generally accepted, even to such an extent that metabolic processes which cannot be proved to occur in any given tissue are not infrequently thought to take place in the liver, although there may be no evidence for such an assumption. The rapidity with which the liver functions in many metabolic processes is not so well known, and failure to realize this fact may be one of the important reasons for some of the contradictory data and conflicting views on liver function. As a concrete example, the diverse data and conclusions concerning the effect of epinephrine on the glycogen content of the liver might be cited. When it is realized that hepatic activity is usually rapid, particularly so in response to many substances such as epinephrine, and that, in many of the investigations, a determination of the glycogen content of the liver was made a considerable time after administration of the epinephrine, the causes for confusion with regard to this question are readily understood.

HEPATIC ACTIVITIES IN RELATION TO THE INGESTION OF FOOD

Gross changes in the liver. The rôle of the liver as the provider of the body begins immediately after the ingestion of food and is definitely portrayed in the difference between its gross appearance in the fasting and digesting states. The liver of the fasting animal appears smaller than is usually considered normal and lacks somewhat its characteristic color. The edges of the organ are sharp. If the fast has extended for a few days, in many species a characteristic fatty appearance develops. The liver of the digesting animal, while affected somewhat differently by various foodstuffs, appears larger than the liver of the fasting animal. It has the characteristic dark-red or pale-red color, depending on the time after food is taken; its tissue is very friable and its edges are slightly rounded. A picture of the most extreme differences which are usually noted can be observed by comparing the liver of an animal of a species that hibernates, when in the digesting state, and that of an animal of the same species after the latter has hibernated for several days. The liver of the former presents the appearance which is usually regarded as normal, whereas that of the latter appears to be in a most extreme fatty condition. The appearance of the liver in the latter instance will again be normal within a remarkably short period after taking food.

The diurnal cycle. The variation of hepatic activity in relation to the ingestion of food has indirectly been quantitated by determination of the major constituents of the organ at various periods of time after feeding. Forsgren (1), using a histologic technic, observed in the livers of rabbits a cyclic activity which he considered to involve the glycogen-forming and bile-secreting functions. He interpreted his observation as indicating that the secretion of bile alternates with the deposition of glycogen, and that these two functions were not regulated merely by nutrition but were probably correlated in some way with a rhythmic activity in the digestive organs. He believed that during the night there was a maximal deposition of glycogen and a minimal formation of bile and that during the day the reverse condition prevailed. He designated these two alternating functions as the "assimilatory" and "secretory" phases of the cycle and concluded that they were not dependent on the ingestion of food.

*Nineteenth McCon Lecture delivered before the Society for Biological Research of the School of Medicine, University of Pittsburgh, April 26, 1935.

†Division of Experimental Medicine, The Mayo Foundation.

Agren, Wilander and Jorpes (2) described cyclic changes in the glycogen content of the livers of rabbits, rats and mice, changes which they believed were largely independent of food intake. Glycogen accumulated in the liver during the night and disappeared to some extent the next morning. Similar conditions occurred even in fasting animals. These authors studied the cyclic variations in the glycogen of the liver of mice and rats under continuous feeding and during fasting, but did not study changes which ensue following a restricted period of access to food and water. Thus Forsgren, Agren, Wilander and Jorpes were of the opinion that the cyclic changes in the liver are independent of feeding but are largely dependent upon astronomic factors.

Higgins, Berkson and Flock (3) noted that when rats were given free access to food, all individuals did not eat at the same time, so that it was not possible under such conditions to have all animals in a large group in the same stage of the digestive cycle. To overcome this difficulty they trained the rats to eat at a definite time by permitting them access to food for a two-hour feeding period from 9 to 11 a. m. After the animals were fed in this manner for a sufficient time, groups of them were sacrificed under standard conditions every two hours for a period of twenty-four hours; the weight of the liver was recorded and a chemical determination was made of some of the major constituents of the liver that might vary with the ingestion of food. They observed that, after the feeding the weights of the liver passed through a series of changes which followed a characteristic form. An increase in the weight of the liver began soon after the taking of food and reached a maximum in the early evening or about six hours after food and water were withdrawn. A transient fall in the weight of the liver was then recorded, followed by a second rise which reached its maximum about 1 a. m. From this time on a gradual decline in weight of the organ occurred throughout the remainder of the night, so that, at 7 a. m., weights were recorded at essentially the prefeeding level of twenty-two hours before. Thus the curve depicting these changes was bimodal. Chemical analysis of certain of the constituents of the liver showed that the changes in the weights of water, glycogen and protein followed a similar rhythmic variation as the total weight of the organ.

Subsequently, Higgins, Berkson and Flock (4) further studied the relation of feeding to these cyclic changes in the liver. They trained groups of rats to eat and drink for two hours progressively for twenty-four hours. Ten rats were trained to eat from 9 to 11 a. m., ten from 11 a. m. to 1 p. m., ten from 1 to 3 p. m., and so forth. After a ten-day training period all rats were sacrificed six hours after eating 10 gm. of food. In preliminary training, duration of feeding, amount of food consumed and time of sacrificing after feeding, all rats were alike. The only varying factor was the time of day the animals were fed. Under these conditions, the curve of changes in the weight of the liver and in its glycogen and water content was practically a straight line.

In a more recent study Higgins (5) determined the changes at two-hour intervals in the weights of the livers of rats that had been maintained in total darkness and on a restricted two-hour feeding period for several weeks prior to the final experiment. He obtained a curve of cyclic changes similar to that found in the first mentioned investigation of Higgins, Berkson and Flock. In other words, the liver underwent changes in weight in relation to the ingestion of food in the case of animals kept in darkness exactly the same as in animals maintained under normal conditions. He also found that the type of curve was affected differently by various foodstuffs.

These studies on the diurnal cycle prove that there is a marked change in the quantity of some of the constituents of the liver in relation to the digestive cycle. It must not be assumed that all such changes involve only the food actually ingested. It is possible that a plethora of foodstuff entering the circulation may cause a rearrangement of previously deposited food stores in the body. However, carefully controlled studies of the diurnal cycle, using food substances that can be labeled such as some of the recently utilized isotopes, offer the possibility of determining more definitely the fate of various foodstuffs and the part the liver plays in their immediate storage and distribution.

Histology and cytology of the liver. While histologic studies of the liver have emphasized the rapid changes that occur in the demonstrable quantity of the important stored foodstuffs, they have given at best but an imperfect picture of what occurs during the sojourn of such stored foodstuffs in the organ. It is relatively easy to demonstrate microscopically a certain amount of glycogen and fat in the hepatic lobule. Protein deposition has not been conclusively demonstrated in the hepatic cell, although Noël (6) described star-shaped granules which he concluded were a deposit form of this foodstuff. It has not been so easy to agree on the manner in which these substances are deposited. According to Noël, all the hepatic lobules are functioning within two hours after the ingestion of food. The current view in regard to the manner in which glycogen and fat are laid down in the hepatic lobule is as follows (7): When glycogen is being formed in increasing amounts in the liver, it appears first and in more abundance in the cells of the lobule adjacent to the central vein and, as more glucose becomes available, the glycogen accumulates in the other hepatic cells, those around the periphery of the lobule being the last to obtain their store. In general, the withdrawal of glycogen takes place in reverse order from the course of its deposition, the cells around the central vein appearing to retain glycogen longest. The distribution of glycogen in the hepatic cell is not uniform but, usually, glycogen granules are not found on the periphery or in the nuclei. The fat deposited in the hepatic lobule presents varied pictures. It is not possible at present to state how much of the microscopically demonstrable fat is part of the fat ingested in the previous meal or fat mobilized from other fat depots of the body. It is also impossible to distinguish without other criteria such as necrosis whether the fat in the hepatic cell is of physiologic or pathologic significance. In general, the fat which appears in the hepatic cell after the ingestion of large amounts of fat occurs in the form of globules, and their distribution in the lobules is quite variable. The fat which is demonstrable in the hepatic cell after injury usually first appears as granules. The amount of fat that can be stored in the hepatic cell and demonstrated microscopically is truly enormous. In a hibernating animal, every cell in the lobule may be so completely distended with fat that the nucleus will be pushed to the outside

of the periphery, giving the so-called signet-ring appearance. It is often possible, particularly in the liver of a fasted animal, to demonstrate large amounts of fat in the cells lining the intrahepatic bile ducts. The significance of this is not known.

Cytologic studies of the liver have demonstrated that definite and rapid changes occur in the hepatic cell, not only in relation to the ingestion or withdrawal of food, but also depending upon the kind of foodstuff ingested. Even a cursory cytologic study of the liver of a carbohydrate-fed animal and of a fat-fed animal will demonstrate characteristic changes differentiating them from each other. It is also possible to differentiate cytologically the liver of a fasted animal from that of a well-fed animal. However, many of the studies of the protoplasmic details of the hepatic cells in relation to the ingestion of food have given contradictory results. There are several reasons for the failure of cytologists to see everything alike, and when the complexity of the hepatic cell and the multiplicity of its activities are taken into consideration, it is rather surprising that there is so much agreement.

In this connection it should be noted that the changes in the hepatic cell are occurring relatively rapidly; that these changes involve elaboration of substances, some to be transferred to the blood or lymph and others to be excreted in the bile; that there is a constant checking-in or checking-out of different kinds of storage material, and that the rate and character of the activity of the hepatic cell at any given time is dependent upon many variable factors which are almost impossible to maintain constant for any great length of time. As an illustration it should be noted that the finer details of the arangement of the protoplasm of an hepatic cell containing little storage material may not be due to any specific change in the structure of the cell but rather to the ability to see such details better in the absence of the storage material. However, if sufficiently extreme conditions of hepatic activity are taken for comparison, definite differences in the cytologic appearance of the hepatic cell in relation to the ingestion of food can be demonstrated, as Altmann (8) showed so many years ago in the livers of frogs in the summer and winter seasons. It is probably expecting too much of the method to corroborate in all their minute details the observations of some cytologists like Noël.

The statements just made in regard to the general cytologic details of the hepatic cell apply with equal force to the special cytologic structures, the mitochondria. The question of the significance of mitochondrial changes in relation to hepatic cell activity is as yet not answered. It appears quite probable that changes in the number, shape and distribution of mitochondria do occur in relation to the ingestion of food; the specificity of such changes, however, is still open to question, although the evidence presented in regard to a relationship between the mitochondrial morphology of the hepatic cell and the glucose-glycogen equilibrium is very suggestive (9, 10). The statement of Kater (11) that the actual explanation for the changes in the mitochondria of the liver which accompany digestion must still be regarded as elusive, expresses the present status of the problem very succinctly. The significance of the Golgi apparatus in relation to hepatic cell activity is still open to question (for a review of the recent literature refer to Weatherford (12)).

I do not wish to leave the impression that histologic and cytologic studies of the liver have been without value or that such studies may not be a profitable method of obtaining new facts in regard to hepatic activity in relation to the fate of the different foodstuffs. As a matter of fact, probably none of the usual methods of investigating the liver, and few that offer more fruitful results, is being used less at present than cytologic research. The main difficulty in the past appears to have been that the cytologists have not employed standard and controlled physiologic procedures. I agree with Kater (11) that, if the results of a cytologic investigation are to be of value, the physiologic data must be as accurate as the cytologic observations. Many of the older researches should be repeated using standard methods of feeding and the newer knowledge of diets. Noël's conclusion, made from his studies on the mouse, that part of all the hepatic lobules are functioning within two hours after ingestion of food, should be investigated using other species of animals. If this conclusion were correct, it would indicate that the variations in hepatic function and hepatic reserve depend on differences in activity of different zones of cells within the lobule and not upon entire lobules, thus signifying that, physiologically, an hepatic trabecula is the functional unit of the liver and not the lobule. In this connection it should be determined beyond any question of doubt in what cells of the trabecula of the liver of the fasted animal glycogen is first formed after the ingestion of carbohydrate, and likewise, the site of the cells in which glycogen is first to disappear in the beginning of a fast. Similar observations should be made in regard to the changes in demonstrable fat in the fasting state and after feeding fat. It should be determined whether the star granules do indicate the deposit of protein as Noël concluded.

It should also be noted that the cytologists have not proved from the physiologic viewpoint that the secretion granules which they consider as bile really is the external secretion of the gland (12). It would be of considerable value to have an accurate cytologic picture of the transformation of the hepatic cell completely filled with fat to the usual type of cell seen when the animal is eating a mixed diet. It is possible that enlargement of knowledge concerning the significance of the mitochondria of the hepatic cell may give an answer to some of the most important questions concerning hepatic function. As an illustration the observations of Kater and Smith (13) can be cited in which they noted the formation of fat globules in the mitochondria after the feeding of cane sugar. This would appear to be suggestive evidence for the long held but never proved theory that the transformation of carbohydrate to fat occurs in the hepatic cell. Finally it should be emphasized that it is impossible to quantitate stored food material as glycogen and fat in the liver by microchemical methods. Any investigator who has attempted to estimate the quantity of these substances in the liver microscopically and had his efforts checked by chemical analysis realizes that he may be 100 per cent wrong.

STORAGE OF FOOD MATERIALS

The liver is the storehouse of utilizable food for the body as a whole. While food is stored in other tissues of the body, such stores are either limited to consumption by the tissues in which they are stored, such as

glycogen in muscle, or are apparently only used when ingested food and the hepatic supply is decreased, such as protein and fat. In this respect the liver can be compared to the pack containing the daily ration on the back of the soldier.

Carbohydrate. It has been known for almost a century that there was a storage form of carbohydrate, glycogen. This substance is normally stored in amounts sufficient to be considered a food depot in muscle and liver. The total amount ordinarily stored in each of these tissues is approximately equal, but the percentage amount is much greater in the liver. While the ultimate fate of a large proportion of the glycogen stored in the two depots is probably the same, that is, of being burned in the voluntary muscles, their physiologic significance is quite different: Only the glycogen in the liver is capable of being transformed into glucose and of being mobilized for direct utilization by all the cells of the body (14).

The amount of glycogen stored in the liver varies within wide limits even in the normal animal depending upon several factors, the most important of which are the amount and character of food ingested, the extent of bodily exertion and the species of animal. Changes in the glycogen content of the liver can occur very rapidly. It would appear to be very rare indeed for the liver to be devoid of glycogen. The maximal amount of glycogen that can be stored in the liver greatly exceeds the amount usually found. Butsch (15) injected large amounts of glucose intravenously into dogs at a constant rate until the glucose tolerance was broken. He found that the liver could store glycogen under the condition of his experiments to a maximum of 20 to 25 per cent. Pollack and associates (16) as well as Soskin and associates (17) have shown that the glucose capacity of the dehepatized animal is much less than that of the normal animal.

Protein. Whether or not there is a form of storage protein similar to glycogen as the storage form of carbohydrate and fat as the storage form of this food substance has been a debated question. A brief review of the more pertinent investigations on the subject has been given by Luck (18). The fate of ingested protein appears to be fairly well determined up to a certain point, but from there on we have at best only conjecture. Protein is absorbed from the gastro-intestinal tract in the form of amino-acids. Most of the amino-acids are stored temporarily in the liver, a small amount in the involuntary muscles (19). A certain proportion of these amino-acids are built back into the body protein of the individual ingesting them. The amounts so utilized depend on many factors, such as whether the individual is growing, the nutritional condition, character of the diet and so forth. The excess amino-acids not thus utilized are deaminized. Under normal dietetic and nutritional conditions in the adult a very high percentage of the amino-acids appears to be deaminized shortly after ingestion. The question is whether or not some of the amino-acids are used to make a special storage form of protein.

The most recent work on this problem is that of Luck (19), which would indicate insofar as the liver is concerned that no single protein or fraction of the hepatic protein can be regarded as reserve material in the sense of being chemically distinct from the basal structural protein of the organ. Luck maintained a group of rats on a low protein diet and another group on a high protein diet. The livers of each group were removed and the basal protein of the organ quantitated under controlled conditions. He found that the rats maintained on a high intake of protein had an increased content of protein per unit weight of hepatic tissue, but that each of the basal protein fractions increased in equal amounts as compared with their values in the livers of rats on a restricted intake of protein. These results would indicate, within the limits of present chemical methods, that all of the hepatic proteins participate equally in the function of storage.

While the evidence is definitely unfavorable to the view that a special deposit form of protein exists, there is no question but that the body may contain a considerable amount of protein which can be used for fuel without seemingly altering the protoplasmic activity of the body cells. Several methods have furnished evidence in regard to the presence of deposit protein, the most important being studies made during fasting, in metabolic diseases, particularly diabetes, and those made by Boothby (20) and his coworkers on thyroxin. In all these conditions there is a period in which nitrogen elimination exceeds nitrogen intake. Probably all the cells in the body are drawn upon for this protein for fuel in time of metabolic stress. The liver appears to be drawn upon more heavily than other tissues of the body. Addis (21) and his coworkers have recently quantitated the total protein lost from various tissues of rats during fasting. They found that after a seven-day fast the amount lost varied from 62 per cent of the total coming from the muscle, skin and skeleton, 16 per cent from the liver, to 0.5 per cent from the heart. On the other hand, the liver lost 40 per cent of its total protein, which was a much greater less than for any other tissue. The same author (22) also found that, after a two-day fast, the liver lost 20 per cent of its original protein whereas other organs lost only 4 per cent. These results definitely indicate that the liver is the site from which protein for fuel is first, and to the greatest degree, withdrawn and that the liver is the true storehouse for protein.

Fat. The fat in the liver is of considerable importance, both physiologically and pathologically. On a well-balanced diet the fat content of the normal liver appears to be fairly constant and, in dogs, is about 2.5 per cent. From 40 to 70 per cent of the hepatic fat occurs in the form of neutral fat, and the rest as phospholipids. The fat content of the liver can be increased by feeding a fatty diet and, if the appropriate diet is fed for a sufficient length of time, the fat content of the liver may become as high as 50 per cent. While the total fat content of the liver may be only a small percentage of the total fat content of the body, the hepatic fat may physiologically be of the greater importance.

Changes in the fat content of the liver occur more slowly than those in the glycogen content and possibly also in the protein content. While this difference in rate of mobilization and demobilization makes it possible for the liver to have both a high glycogen and fat content, in general (22) when the hepatic content of one of these storage materials is increasing the other is decreasing, so that they can be said to have a reciprocal relationship to each other.

The fat content of the liver increases in the fasting state provided there is available fat in other fat depots of the body. Hepatic fat is also greatly in-

creased if fat is available in many pathologic states, particularly some of those affecting metabolism and after the administration of hepatotoxic agents such as chloroform or carbon tetrachloride. Alcohol in amounts that cause no change in the livers of animals on a well-balanced diet will cause rapid deposition of fat in the liver when a fatty diet is fed. Sufficient (23) has been stated to show that the liver is a fat depot and that hepatic activity is significant in fat metabolism.

Miscellaneous storage substances. There are possibly numerous important storage substances in the liver, the existence and significance of which are unknown. It is known that hepatic tissue has a high content of certain minerals. While some of these minerals are probably in the hepatic cells, others like iron are found mainly in the stellate cells. There are some data suggesting that the liver may store other substances in a similar manner as it does vitamin D and the active fraction in pernicious anemia.

There is considerable difference of opinion concerning the significance of the variation of the water content of the liver. In most of the discussions of the subject it has not been realized that the liver is probably never doing just one thing, and that the total water content of the organ is a resultant of all the processes occurring at that time. It is obvious, since usually the water content of the liver is high, being approximately 70 per cent, that if another substance accumulates in the organ in very large amounts, such as fat, the percentage of water will necessarily decrease. While in all probability the water content of the liver varies in relation to its various physiologic activities (24) just as in any other tissue, there remains the possibility that the liver has a special function in water metabolism. The literature has recently been noted by Crandall and Roberts (25).

MANUFACTURE OF FOOD MATERIAL

Many food substances pass the barrier of the intestinal mucosa and are absorbed in a form either not capable of being utilized directly by the tissue cells or not utilized as readily as in another form to which they can be converted. It is obvious that some tissues of the body must have the ability to make such conversions. In the case of several substances the conversion occurs in the liver.

Carbohydrate. There is considerable difference in the utilization of the more important sugars that reach the blood stream. Glucose is the sugar of choice for burning in the tissue cells. The liver is of importance in relation to this sugar as regards control of its concentration in the blood and storage, both processes being discussed elsewhere. Levulose can be used directly by the body, as has been proved by experiments with the dehepatized animal (26) although, normally, the liver probably transforms the ingested levulose into glycogen before utilization by the tissue cells. Experiments with the dehepatized animal would indicate that only a small amount, if any, galactose is utilized directly, and that the liver is responsible for transforming it into the more preferable glucose, probably first building it into glycogen (27).

Protein. As previously stated, the amino-acids absorbed from the intestinal tract are stored temporarily, for the most part in the liver and in muscle tissue. The amino-acids which are not used as such to repair tissue cells or to form new proteins are deaminized; the nitrogenous portion is converted into urea and the remaining portion is burned or converted as carbohydrate. The manufacture of carbohydrate from amino-acids as well as the formation of the nitrogenous portion into a form capable of being readily excreted are functions of the liver (28).

Fat. One of the most mooted questions in metabolism is how fat is burned. I shall discuss only those phases of the problem which for the most part center around the question of possible transformation of fat to carbohydrate, because investigations on this problem intimately involve functions of the liver that have been discussed. Two opposite schools of thought have developed in regard to the question of such a transformation, each at one time upheld in this country by an able sponsor, MacLeod being in favor and Lusk against the view that such a process occurred in the body. I believe that the most vivid memories that many of us possess of these two great physiologists, picture them in stirring debate over this question. Lusk obtained data for his viewpoint from his numerous studies on the metabolism of the phlorhizinized dog (29). In such studies the respiration quotient (R. Q.) and dextrose-nitrogen (D. N.) ratio were considered significant constants. MacLeod, accepting the implication in the original Myerhoff-Hill theory of muscle contraction but questioning the value of the R. Q. and D. N. ratio in the sense that Lusk meant them, relied for proof of his viewpoint on various researches dealing with depancreatized and dehepatized animals and on the action of insulin and epinephrine, and so forth. MacLeod (30) several years ago summed up the complete evidence in favor of the view that fat is transformed into carbohydrate before being burned and very little of significance has been added since.

It is now considered that much of the evidence marshalled in favor of each viewpoint is of questionable value in relation to the problem. The phorhizinized dog does appear to metabolize some carbohydrate (31-33); the R. Q. and D. N. (30-34) ratio are capable of other interpretations than that made by Lusk and they may not mean what he thought they did. On the other hand, much of the evidence that MacLeod accumulated in favor of the theory has also been questioned, even the investigation which he considered unassailable, namely, the experiments of Chaikoff and Weber (35) on the effect of epinephrine on the sugar excretion in diabetes. These investigators injected epinephrine into well-fattened, fasted, depancreatized dogs, previously treated with insulin but diabetic at the time of experimentation. More sugar was excreted in the urine than could be accounted for from their estimation of the glycogen stores of the body at the time of injection and from the protein and glycerol metabolized. The logical conclusion was that the excess sugar could have come only from fat. Subsequent investigators found, however, that when the glycogen store in liver and muscle was actually measured in experiments otherwise exactly similar to those of Chaikoff and Weber, all the excreted sugar could be accounted for without hypothesizing a source of part of it from fat (36).

In general the problem is unanswered in its entirety, although there is some recently adduced suggestive evidence on both sides. Drury and McMaster (37) maintained rabbits on a fat diet and then removed the liver. Such dehepatized animals retained an R. Q. which suggested that they were burning fat. Murlin

(38) and associates showed that a transformation of fat to carbohydrate does occur in certain plants. Soskin (39) has interpreted some of the results of his studies on the hypophysectomized animal as supporting this theory. At present it must be concluded that the possibility of the transformation of fat to carbohydrate exists, but evidence is lacking as yet that it actually occurs in the animal organism (40). Probably the most significant statement that can be made in regard to the problem is the one attributed to Pflüger: the farmer feeds his swine carbohydrate in the form of corn and sells it in the form of lard; carbohydrate is undoubtedly changed to fat and there remains the possibility that the reverse can occur.

I have discussed the possible transformation of fat to carbohydrate out of proportion to its proved significance for two reasons: (1) because if it actually occurs it is highly probable that hepatic activity will be found to be involved in the process, and (2) because the question is of such great significance, not only in regard to metabolism but also in relation to hepatic physiology, that continued research is indicated. It is possible that investigations employing the use of appropriate isotopes and studies on animals with one or more of the ductless glands which so profoundly affect metabolism removed will afford an answer.

MECHANISM OF REGULATION

It has previously been emphasized that: (1) the body cells constantly require food materials, reaching them in accordance with their varying needs, and (2) that the liver is an indispensable storage and manufacturing plant for these food materials. There must be some mechanism or mechanisms for regulating: (1) the kind and amount of food substances sent to the tissues to meet their changing requirements, (2) the formation of glycogen and glycogenolysis in the liver, and (3) the manufacture of available food materials in the organ as gluconeogenesis from protein and possibly from fat.

Carbohydrate. Very little is known concerning the intracellular mechanism which transforms various substances into a storage form of carbohydrate, glycogen, and subsequently breaks it down into a transportable and utilizable form, glucose. These processes are in all probability carried out by cellular enzymes, but the chemical steps in the processes and regulation of the rate of glycogen formation and glycogenolysis are at present only conjectural (Cori (41) has given a review of literature).

Considerable is known concerning the importance of the liver in furnishing a constant supply of glucose to the tissues of the body. When the liver is removed from an animal, the glucose concentration of the blood immediately begins to decrease (42). When the glucose concentration has decreased to a low level, the characteristic symptoms of hypoglycemia supervene and, if glucose is not administered, fatal coma develops (43). It is rather discouraging to note that little more is known concerning the cause of the symptoms of hypoglycemia and their rapid alleviation by glucose than was known when Magath and I gave the results of our observations on the dehepatized animal many years ago, despite the fact that insulin has subsequently been found to reproduce an identical condition and symptoms with restoration following the administration of glucose, which has been observed thousands of times both in the case of human subjects and animals, and despite the fact that many clinical cases of hypoglycemia, probably resulting from various causes, have been described. It appears evident that the development of symptoms of hypoglycemia depend not so much on the level of glucose as on the rate at which glucose leaves the blood stream. It has also been proved that hyperglycemias depend upon hepatic activity. Hyperglycemia will not occur in a dehepatized animal following removal of the pancreas, during asphyxia, or after the administration of ether, epinephrine or other substances, or after procedures which increase the blood sugar in an animal possessing a liver (44).

As previously stated, the fate of glycogen in the muscle and liver is different. The glycogen in the muscle is converted into lactic acid and thus fulfills its function in relation to the process of muscle contraction, whereas the glycogen in the liver is converted into glucose and is available to all the tissues of the body. The fate of the excess lactic acid, produced during muscular contraction, which reaches the blood stream is not definitely known. It is undoubtedly true, as Cori (45) and Cori (46) and others have enunciated, that some of the lactic acid passes to the liver where it is rebuilt into glycogen. However, Bollman and I (47) have found that large amounts of lactic acid can be injected into a dehepatized animal which subsequently cannot be found in either the blood or urine. Evidently there is a mechanism for taking care of lactic acid outside the liver.

Protein. Very little can be added concerning the mechanism of protein metabolism relative to the liver than has been given. It should be noted that the liver is important in purine metabolism because the uric acid not excreted in the urine is changed to allantoin in the liver (48).

Fat. In the discussion of fat storage in the liver it was pointed out that the changing fat content of the liver, while occurring more slowly than the changes in glycogen content, was of sufficient magnitude and rapidity to indicate that the liver was an important organ in fat metabolism. Knowledge concerning the mechanism of regulation of the mobilization and demobilization of fat in the liver is as yet meager, although a few important advances have recently been made.

The workers in MacLeod's laboratory at the time they were investigating the action of insulin found that it was necessary to provide fresh pancreas in the diet of depancreatized dogs in order to enable them to live for more than a few months. If pancreas was not fed, the animals died and an excessively fatty liver was the only postmortem finding of note. The feeding of raw pancreas prevented the development of the fatty condition of the liver and death (49). Best (50) and his coworkers, in attempting to determine the constituent in the pancreas which prevented the development of the fatty liver, found that it was in the phospholipid fraction and eventually identified it as choline. They found that they could use the rat for studies on fat exchange in the liver, and they have proved conclusively that choline may be an important substance in the mechanism of regulating the fat content of the liver. By feeding an appropriate diet they could increase the fat content of the liver to a large amount. If sufficient choline was added to the diet, which was otherwise not altered, the fat content of the liver did not increase. Furthermore, if choline was added to

the diet of an animal possessing a liver with a high fat content, the fat was quickly demobilized.

Dragstadt, Van Prokaska and Harms (51) have made an extract of pancreas which does not contain choline, but which also causes rapid demobilization of hepatic fat. Bollman (52) has corroborated these findings of Draagstadt, using dogs in which the fat content of the liver was enormously increased by feeding a fat diet in conjunction with the administration of alcohol. The administration of the extract of Dragstadt greatly accelerated the rate of fat demobilization under such conditions.

The forementioned investigations probably dealt mainly with the neutral fat in the liver, which amounts to approximately 70 per cent of the total fat content of the organ. Flock, Bollman and I (53, 24) have attempted to determine the changes in the phospholipid content of the liver under varying dietetic conditions and experimental procedures. A considerable part of our efforts were necessarily directed toward methods of quantitation and experimental procedures as free as possible from the numerous sources of error encountered. Very few positive statements can be made at present. The total phosphate content of the liver remained remarkably constant under most of the conditions studied, the most marked change being a decrease with a high fat diet that produced extremely fatty livers. Of the important phosphate fractions of the organ, the phospholipids varied least.

I have attempted to convey in this brief review (1) that the exchange of fat in the liver is an extremely important process, (2) that it is difficult of investigation, and (3) that some progress is being made, although not commensurable to the importance of the subject.

HEPATIC ACTIVITY AND GENERAL METABOLIC PROCESSES

While the mechanisms regulating the passage of foodstuffs to and from the liver are not known, it is justifiable to postulate that they exist and that the utilization of food by the tissues is closely correlated in some manner with hepatic activity. There are suggestive evidences that variations in the kind and amount of food utilized by the tissues are reflected in changes in the functions of the liver. Investigation of these possible mechanisms is difficult because, in order to evaluate the kind and rate of utilization of the various foodstuffs in the body, reliance must for the most part be placed on the respiratory quotient, an interpretation of which has been called into question. However, there are some data on the question which are suggestive and interesting.

It requires 0.25 gm. of glucose per kilogram of body weight to maintain the normal concentration of glucose in the blood of a dehepatized animal, which previous to operation had been on a normal diet, for the first few hours after loss of the liver (54). This can be interpreted as meaning that a normal animal on a mixed diet requires such an amount of glucose. Care must be used in such an interpretation because factors other than the normal utilization of glucose appear to be present. While 0.25 gm. of glucose per kilogram of body weight will maintain the blood sugar at the normal level for the first few hours after removal of the liver, it soon is necessary to increase the amount of glucose until, thirty hours after operation, it usually requires 1 gm. of glucose to maintain the animal in normal condition. If the animal has been kept on a high carbohydrate diet before removal of the liver, it usually requires a larger amount of glucose initially, whereas if the animal has been fasted for a considerable period of time prior to operation, the glucose requirement is less than if a standard mixed diet had been used. Furthermore, when the liver is removed, the respiratory quotient increases toward unity (55), possibly indicating that the dehepatized animal meets its energy needs with a larger percentage of carbohydrate than the normal animal. The specific dynamic action of glucose and amino-acids varies from normal in the dehepatized animal. The specific dynamic action of a given amount of glucose is enhanced in the animal without a liver as compared with the results obtained in the same animal before removal of the liver (55). On the other hand, injected amino-acids do not cause a specific dynamic action in the dehepatized animal (56).

Other more or less uncorrelated facts could be cited, but sufficient has been given to illustrate the complexity of the metabolic processes in which the liver has a part and that hepatic activity responds to the varying metabolic needs of the organism. I believe it can be accepted as a general conclusion that the liver probably does not control any of the metabolic processes but simply responds to the changing metabolism of the organism as a whole.

RELATION OF HEPATIC ACTIVITY TO THE VARIOUS ORGANS OF INTERNAL SECRETION

It has been considered for many years that the functions of the organs of internal secretion have to do mainly with various phases of metabolism, but only recently have adequate data been presented to demonstrate the complexity of the mechanisms involved. Such data deal mainly with the results of studies on animals from which one or more of the glands of internal secretion have been removed. It would diverge too far from our purposes if more than a brief review of these data were presented, even if knowledge of the subject were not in such a bewildering state as at present. However, since the liver is so important in many metabolic processes, and since the loss of one or more of the glands of internal secretion affects some of the phases of metabolism in which the liver is involved, a few statements of apparently known facts should be given:

Removal of the pancreas, as was learned half a century ago, produces the marked hyperglycemia and glycosuria of pancreatic diabetes. Removal of the hypophysis results in failure to maintain carbohydrate during fasting (57). Removal of both adrenal glands is said to be followed by hypoglycemia and a marked reduction in glycogen in muscle and liver (58). Such findings have only occasionally been noted in our laboratory in adrenalectomized dogs. Removal of the pituitary (59) and the adrenals (60) from a depancreatized animal restores the diabetic animal to a more nearly normal condition as regards carbohydrate metabolism, that is, there is a marked reduction of glycosuria together with its disappearance on fasting, a marked reduction of nitrogen excretion during fasting, and almost complete disappearance of acetonuria and acidosis. These results have been explained in various ways and probably the best theory is that loss of the pituitary and adrenals decreases the rate of

gluconeogenesis from protein or fat in the liver. This theory is as yet not proved.

While much more could be written in regard to the recent work on this phase of the subject, this brief and incomplete review should suffice to illustrate the complex mechanisms of metabolism in which hepatic activity is probably either directly or indirectly a part. It is impossible to say how liver function is affected by various hormones, although a few general statements can be made. Hepatic activity can be changed by hormones in the following respects: (1) by an effect on the rate of body metabolism, (2) by an effect on the intrinsic mechanism of the liver, either for storage or manufacture of food, and (3) by an effect on the amount of available food materials reaching the liver. At any rate it is evident that a great discovery in metabolism will have been made when the rôle of the liver in relation to the action of the various hormones on metabolic processes has been explained.

MISCELLANEOUS ACTIVITIES OF THE LIVER

There are many physiologic processes in the body which, mainly because of lack of definite information concerning them, are said to occur in the liver or said to be due to hepatic activity. While several of such processes might be discussed, only a few in which it appears highly probable that the liver is actually involved and which are pertinent to our subject will be presented:

Cholesterol. One of the most outstanding of these enigmas is cholesterol. The liver is undoubtedly a factor in cholesterol metabolism because this substance is one of the important constituents of bile. But in spite of the large number of investigations and their resulting theories of cholesterol metabolism the rôle of the liver in this process is conjectural.

Bile salts. Considerably more is known concerning hepatic activity in the metabolism of bile salts than in that of cholesterol. A résumé of the literature on the metabolism of bile salts has been given by Sterner, Bartle and Lyon (61). Whipple and Smith (62) concluded from their studies on animals with complete biliary fistulas that bile salts are constant under constant dietary and physical conditions, that dietary factors may affect the amount of bile salts formed, that bile salts administered by vein or by mouth are rapidly and quantitatively excreted in the bile, that the liver is responsible for the elaboration of bile salts, and that slight injuries to the liver may greatly reduce the amount of bile salts formed and excreted. Bollman and I (63) investigated the metabolism of bile salts under various experimental conditions and obtained the following results: The normal dog excretes but traces of bile salts in the urine, and bile salts are not definitely detectable in normal blood. Following intravenous injection of glycocholates or taurocholates only a small portion appears in the urine and the injected material rapidly disappears from the blood. After continuous administration of large amounts of bile salts the indication is that destruction of these substances takes place, since only traces are found in the urine in feces. After complete removal of the liver, bile salts are not found in the blood or urine even after periods of time in which they are readily detected following ligation of the common bile duct. The liver appears to be the site of formation of bile salts. After complete removal of the liver, injected bile salts are rapidly excreted in the urine, so that quantitative recovery of the injected material is usually made within twelve hours. If similar injections are made in animals with biliary obstruction, only part of the injected material can be recovered. The liver apparently plays a predominant part in the destruction of bile salts. The formation of bile salts is inhibited by administration of hepatotoxins such as chloroform, carbon tetrachloride, or tetrachlorethane, but is not affected by other toxins such as toluylendiamine. Destruction of bile salts is little altered by hepatotoxins that markedly alter the formation of bile salts.

Blood proteins. The relation of the liver to the formation of the blood proteins is another disputed question. A fine review of the investigations on this problem has recently been made by Reimann, Medes and Fisher (64). The conclusions made from the results of the large number of researches on the question are remarkable mainly because of their contradictions. However, when all the evidence is considered, it appears probable that the liver is in some manner involved in the formation or mechanism of regulation of the blood proteins, particularly fibrinogen (65). It is either not the sole site of their formation, or other tissues have the capacity of storing them in relatively large amounts. It is possible, as Reimann, Medes and Fisher suggest, that the liver is responsible for elaboration of protein precursors of the blood protein, which are incorporated in widely-distributed cells. It is evident that more research is required before the rôle of the liver in such processes as edema and coagulation of the blood can be enunciated.

Ketone bodies. The liver is an important, and possibly the only site of formation of the ketone bodies. It has been found that these substances rapidly disappear from the blood of diabetic animals after removal of the liver (66). They have also been noted to be formed from appropriate precursors when the latter were perfused through the liver (67). As previously noted, their production is decreased in the diabetic animal from which the pituitary or adrenals are removed. The mechanism and physiologic significance of their formation are as yet debated.

Heparin. Heparin, which was discovered by Howell and Holt (68), appears to be a definite product of hepatic activity. Whether its origin in the liver can be in any way related to the possible origin of fibrinogen at the same source is open to speculation.

Anti-anemic factor and hemoglobin. The presence of the anti-anemic factor in such large amounts and the potency of liver tissue in the restoration of hemoglobin, as the excellent investigations of Whipple and Robscheit-Robbins (69) and others have proved, indicates that the liver is of great importance in pigment metabolism.

RELATION OF HEPATIC ACTIVITY TO DISEASE OF METABOLISM

The liver has a necessary part in so many of the processes of normal metabolism that it would appear justifiable to conclude that the organ is involved in many of the diseases of metabolism. In all probability it is rare that hepatic impairment is the primary cause of the disease, but rather that disturbances in the processes of normal metabolism produce changes in hepatic activities in order to meet the altered metabolic requirements of the body. The subject of the relation of hepatic activity to the various diseases of

metabolism requires summarization of existing data and further research before accurate conclusions can be made. However, there are a few outstanding examples of metabolic disease, of which diabetes is probably the best, in which the liver is signally involved. As was previously stated, the hyperglycemia of the depancreatized animal depends upon activity of the liver and the hypoglycemia due to insulin will occur without the presence of the liver, although restoration of the blood sugar after the administration of insulin depends upon the liver. It is as yet questionable whether insulin has a direct action on the liver and whether hepatic activity in pancreatic diabetes is anything more than the response for an increased need of glucose to maintain a hyperglycemia in the presence of tremendous losses of sugar. In view of the proved necessity of the liver for maintaining the known hyperglycemias, it is reasonable to suppose that if forms of diabetes other than pancreatic diabetes *do* exist, as seems probable, the liver is also involved in those instances in which they occur.

Other examples than diabetes could be given, but sufficient evidence has been presented to justify the statement that, in many of the alterations of the processes of normal metabolism, hepatic activity responds to meet the changing needs of the body for a constant supply of food. Investigation of liver function in the various diseases of metabolism offers a fruitful field of research, but it awaits the development of more accurate methods of quantitation.

EFFECT OF DECREASED HEPATIC TISSUES ON LIVER FUNCTION

There are several methods of decreasing the amount of hepatic tissue. The remaining hepatic substance may be normal, atrophic, or cirrhotic, depending upon the method used to decrease the size of the organ (71). Regardless of how the hepatic tissue has been decreased, the functions of the organ, which have been previously given, persist in an apparently normal manner even with relatively small amounts of hepatic tissue. It requires less than 20 per cent of the normal amount of the organ to maintain its functions (72).

CONCLUSIONS

I have assumed that the purpose of the Mellon Lecture was not only to present the results of recent investigations on a specified subject, but also to review, evaluate, and attempt to correlate the significant and applicable existing data in such a manner that the imagination would be stimulated, giving birth to renewed efforts of inquiry. With considerable misgivings I have attempted to do this in regard to the rôle of the liver in the mechanism of maintaining a constant supply of utilizable food materials for the body tissues. While only partial success has been attained, I believe that sufficient evidence has been presented to indicate the importance of the liver in this mechanism, that hepatic activity must be considered as a possibility in every phase of metabolism, and that existing knowledge of the subject is only a small percentage of what must be learned before all the intricate processes involved are fully understood.

I should like to leave with you a picture of the liver as a large storage and manufacturing plant, constantly teeming with activity. Through its vast sinusoids, which are in intimate relationship with the multitude of hepatic cellular units, are transported the various materials upon which the tissues of the body must rely for their source of energy, growth, and repair and for the necessities for maintaining the processes of life. Some of these substances are capable of being used directly by the tissue cells and the liver only stores them during periods of plethora. Other substances are more crude and the liver transforms them into a utilizable form. One must imagine that within the hepatic cell are tools, probably enzymes, for making possible the storage and manufacture of these essential substances. Coming to the hepatic cells must be numerous chemical messengers to correlate hepatic activity to the varying needs of the body. Finally it should be noted that this vital stream to and from the liver must persist, even during dearth of material, bodily disease, and hepatic impairment, as long as life exists. Surely the liver can rightfully be called the provider of the body.

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Phenolphthalein as a Dilution Indicator in Gastric Analysis*

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IT is generally recognized that the acidity of a specimen of stomach contents, obtained in the course of a gastric analysis, is not a true measure of the gastric response under the conditions indicated. This is so because each such sample contains a variable and indeterminate proportion of the original test meal as well as of saliva and regurgitated duodenal contents. For example, in the course of a Rehfuss series the proportion of test meal present in any one gastric sample may vary from zero to 80 per cent or more of the total volume, according to Bloomfield and Keefer (1), whereas in the one hour specimen obtained by the single aspiration method, Gorham (2) has reported the presence of as much as 60 per cent of the original test meal. As yet we possess no satisfactory technique for evaluating the second and third of these contaminants, but dilution by the test meal can be estimated very simply. For this purpose, it is necessary only that the test meal contain some non-toxic substance, the concentration of which can be measured easily and reliably, and which is known not to be lost in the stomach either by absorption or by chemical combination. A variety of such substances, designated as *dilution indicators*, have been proposed from time to time and in some cases used quite extensively. One of these is phenolphthalein (Lanz (3), Bloomfield and Keefer (4)), the concentration of which can be estimated with a precision of 1 per cent by adding a uniform amount of alkali (e.g., 1 ml. of 0.1 N NaOH to 10 ml. of solution) to convert it to the red alkali salt, and then comparing the color intensity with that of a solution of known concentration in a colorimeter. Because of its obvious advantages over other dilution indicators, especially the fact that it is colorless at pH values less than 8 and therefore will not interfere with the use of other titration indicators for the determination of free and total acidities, we decided to employ it in a series of investigations which were being planned.

It is generally known that the solubility of phenolphthalein in neutral and acid aqueous solutions is rather low. For distilled water, Fantus and Dyniewicz (5) give values of 0.3 mgm. per 100 ml. at 25° C. and 0.6 mgm. per 100 ml. at 38° C.; in 7 per cent alcohol, the solubility at 25° is about 0.8 mgm. per 100 ml. (by interpolation). On the other hand Utz (6) is quoted as having reported a value of 2 mgm. per 100 ml. in neutral water at ordinary temperatures and about 20 mgm. per 100 ml. "when warmed." We were unable to verify these latter values because the original refer-

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ence was not available to us,† but since phenolphthalein had been reported by others as being satisfactory we assumed that no difficulty need be anticipated in respect to its low solubility in non-alkaline solutions.

Concerning the standard of reference employed in these experiments: In general, alkalinized phenolphthalein is known to lose color on standing (Lund (9), Thiel (10)), due probably to the conversion of the red

TABLE I

Illustrative experiment to show the loss of indicator from an alcohol-phenolphthalein test meal on standing

Time interval (hours)	0	½	1	1¾	2¼
Concentration of phenolphthalein (mgm. per 100 ml.)	10.0	8.0	7.8	7.4	6.7
Loss of phenolphthalein (per cent of the initial value)	0	20	22	26	33

Accordingly, we prepared a test meal of 7 per cent alcohol which contained 0.01 per cent (10 mgm. per 100 ml.) of phenolphthalein, by diluting a 1 per cent solution in 95 per cent alcohol with the requisite amount and concentration of dilute alcohol, following the procedure employed by previous workers. The immediate result was a clear solution without any evidence of precipitation, but at the end of one hour a portion of the test meal which had been retained as a standard of reference for colorimetry showed a distinct settling out of a white solid. By the end of a second hour, this precipitation had become considerable and contact of some of the solid with alkali left no doubt of its being phenolphthalein. Such a precipitation of the indicator, if it occurs directly from the alcohol test meal, is certain to occur also on dilution of the latter with water and particularly with acid stomach contents — thus completely invalidating the use of this substance as a dilution indicator.

In order to confirm the above observation, therefore, the following experiment was performed. A stock solution of the alcohol-phenolphthalein test meal was prepared in the usual way. From time to time a sample of this stock solution was drawn off, filtered rapidly, alkalinized, and compared in the colorimeter with a standard solution of the initial concentration which had been similarly alkalinized. To insure the development of maximum color on alkalinizing, enough NaOH was added to bring its final concentration up to 0.01 N, corresponding to a pH of *circa* 12 (Michaelis and Gyemant (8)). Since the temperature and the conditions of movement of the reaction flask were not controlled, an experiment such as this one is not quantitatively reliable in respect to the kinetics of precipitation, but it is none-the-less adequate for our present purpose. The results of a typical experiment of this kind, summarized in Table I, leave no doubt of the validity of our initial observation regarding the progressive precipitation of the indicator; in the first half hour the loss of solute was 20 per cent of the initial concentration, and it increased progressively thereafter. There is no apparent reason for expecting that this precipitation will not occur in the stomach as well as *in vitro*. Part of the solid will remain behind in the gastric cavity; but even that disproportionate amount of solid phenolphthalein which may be withdrawn with each specimen will be filtered or centrifuged off with the mucin and other solids and thus lost in the determination. In view of this irregular and unavoidable loss, it must be concluded that phenolphthalein cannot be employed as a dilution indicator.

†We have since discovered that Seidell (7) quotes Utz as reporting a value of 2 mgm. per 100 gm. in neutral water.

di-sodium salt in the quinoid form to the colorless trisodium salt. That the rate of loss of color is relatively great even when the concentration of alkali is as low as at pH 12, may be seen from the experiment illustrated in Table II. In the first half hour of standing

TABLE II

Experiment to illustrate the loss of color of alkalinized phenolphthalein (10 mgm. per 100 ml.) on standing in 0.01 N NaOH, as determined by comparison with freshly prepared standards of reference*

Time interval (hours)	0	½	1	3½
Colorimeter reading	20.0	22.0	22.8	24.6
Loss of color (per cent of the initial value)	0	10	14	23

*This is estimated to be the lowest concentration of alkali which will effect complete conversion of the phenolphthalein to its red salt form, and corresponds to pH 12.

at room temperature, one such solution lost as much as 10 per cent of its initial intensity of color; after the second half hour, this loss had increased to 14 per cent. Consequently, in the experiments similar to that of Table I it was not possible to employ the same portion of solution as colorimetric standard throughout the entire series of observations. Instead, a fresh color standard was prepared simultaneously with each of the unknown solutions, and readings were made with sufficient rapidity to eliminate any significant amount of this decolorization in either the standard or the unknown. This spontaneous decolorization of the alkalinized phenolphthalein acquires further significance by reason of the fact that, unless the unknown solutions as well as the standards of reference are alkalinized only a short time before being read, the phenomenon may constitute another source of error of considerable magnitude.

CONCLUSION

We have demonstrated the existence of two possible sources of error in the use of phenolphthalein as a dilution indicator in gastric analyses. (1) The solubility of phenolphthalein in the acid form, both in water and in dilute alcohol, is considerably lower than the concentration which it is necessary to employ in a test meal. Even if the latter be prepared immediately before it is administered to the subject, in the course of a two hour Rehfuss series determination a considerable amount will be lost by precipitation in the stomach and by filtration of the specimens to remove mucin and other solids preparatory to colorimetry. (2) Phenolphthalein, at a concentration of 10 mgm.

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Accordingly, we prepared a test meal of 7 per cent alcohol which contained 0.01 per cent (10 mgm. per 100 ml.) of phenolphthalein, by diluting a 1 per cent solution in 95 per cent alcohol with the requisite amount and concentration of dilute alcohol, following the procedure employed by previous workers. The immediate result was a clear solution without any evidence of precipitation, but at the end of one hour a portion of the test meal which had been retained as a standard of reference for colorimetry showed a distinct settling out of a white solid. By the end of a second hour, this precipitation had become considerable and contact of some of the solid with alkali left no doubt of its being phenolphthalein. Such a precipitation of the indicator, if it occurs directly from the alcohol test meal, is certain to occur also on dilution of the latter with water and particularly with acid stomach contents—thus completely invalidating the use of this substance as a dilution indicator.

In order to confirm the above observation, therefore, the following experiment was performed. A stock solution of the alcohol-phenolphthalein test meal was prepared in the usual way. From time to time a sample of this stock solution was drawn off, filtered rapidly, alkalinized, and compared in the colorimeter with a standard solution of the initial concentration which had been similarly alkalinized. To insure the development of maximum color on alkalinizing, enough NaOH was added to bring its final concentration up to 0.01 N, corresponding to a pH of over 12 (Michaelis and Gyemant (8)). Since the temperature and the conditions of movement of the reaction flask were not controlled, an experiment such as this one is not quantitatively reliable in respect to the kinetics of precipitation, but it is none-the-less adequate for our present purpose. The results of a typical experiment of this kind, summarized in Table I, leave no doubt of the validity of our initial observation regarding the progressive precipitation of the indicator: in the first half hour the loss of solute was 20 per cent of the initial concentration, and it increased progressively thereafter. There is no apparent reason for expecting that this precipitation will not occur in the stomach as well as *in vitro*. Part of the solid will remain behind in the gastric cavity; but even that disproportionate amount of solid phenolphthalein which may be withdrawn with each specimen will be filtered or centrifuged off with the mucin and other solids and thus lost in the determination. In view of this irregular and unavoidable loss, it must be concluded that phenolphthalein cannot be employed as a dilution indicator.

†We have since discovered that Seidell (7) quotes Utz as reporting a value of 2 mgm. per 100 gm. in neutral water.

di-sodium salt in the quinoid form to the colorless trisodium salt. That the rate of loss of color is relatively great even when the concentration of alkali is as low as at pH 12, may be seen from the experiment illustrated in Table II. In the first half hour of standing

TABLE II

Experiment to illustrate the loss of color of alkalinized phenolphthalein (10 mgm. per 100 ml.) on standing in 0.01 N NaOH, as determined by comparison with freshly prepared standards of reference*

Time interval (hours)	0	½	1	3½
Colorimeter reading	20.0	22.0	22.8	24.6
Loss of color (per cent of the initial value)	0	10	14	23

*This is estimated to be the lowest concentration of alkali which will effect complete conversion of the phenolphthalein to its red salt form, and corresponds to pH 12.

at room temperature, one such solution lost as much as 10 per cent of its initial intensity of color; after the second half hour, this loss had increased to 14 per cent. Consequently, in the experiments similar to that of Table I it was not possible to employ the same portion of solution as colorimetric standard throughout the entire series of observations. Instead, a fresh color standard was prepared simultaneously with each of the unknown solutions, and readings were made with sufficient rapidity to eliminate any significant amount of this decolorization in either the standard or the unknown. This spontaneous decolorization of the alkalinized phenolphthalein acquires further significance by reason of the fact that, unless the unknown solutions as well as the standards of reference are alkalinized only a short time before being read, the phenomenon may constitute another source of error of considerable magnitude.

CONCLUSION

We have demonstrated the existence of two possible sources of error in the use of phenolphthalein as a dilution indicator in gastric analyses. (1) The solubility of phenolphthalein in the acid form, both in water and in dilute alcohol, is considerably lower than the concentration which it is necessary to employ in a test meal. Even if the latter be prepared immediately before it is administered to the subject, in the course of a two hour Rehfuss series determination a considerable amount will be lost by precipitation in the stomach and by filtration of the specimens to remove mucin and other solids preparatory to colorimetry. (2) Phenolphthalein, at a concentration of 10 mgm.

per 100 ml. and a pH of about 12, the lowest pH value compatible with maximum conversion of the indicator to its red salt form, loses color at a significant rate. The second of these errors can be obviated by not alkalinizing the phenolphthalein solutions until just before they are introduced into the colorimeter cups for reading, but the first error constitutes an insurmountable barrier to the use of the substance as a dilution indicator. It follows, therefore, that all previous work based on the use of phenolphthalein in this way involves one or both of these errors unless otherwise demonstrated and should be repeated with the aid of a more reliable substance. To this end we have investigated phenol red. Our results indicate that this indicator possesses neither of the disadvantages of phenolphthalein, since it is soluble in the acid form and the rate of decolorization of the red alkali salt at pH 11-12 is so slow as to be insignificant. A preliminary report of this work has already been published (Hollander, Penner and Saltzman (11)).

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The Effect of Ephedrine on the Secretion of Acid by the Human Stomach*

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CHEN (1) in 1926 reported that in two dogs with Heidenhain pouches and three with Pavlov fundus pouches, ephedrine given subcutaneously or intravenously increased the gastric secretions both in volume and acidity. This increase was very slight, less in fact, than that after a meal. There was no difference in the two types of pouches. Results of a number of experiments have been reported on the effect of ephedrine on the movements of the stomach *in situ* in animals. These, in general, suggest a relaxation with inhibition of peristalsis (2, 3, 4). Fray (5) made a roentgenological study of the effect of ephedrine upon the human stomach. He observed that ephedrine, in the vast majority of cases, produces a diminution in peristalsis and tone of the stomach free of local disease. Van Liere, Lough and Sleeth (6), in 1936, determined fluoroscopically that ephedrine in therapeutic doses produces a marked prolongation in the emptying time of the healthy human stomach. Hellebrandt (7) reported that a definite relation may be demonstrated between the motor and secretory function of the human stomach. The acidity of the gastric contents increases as the motility augments and subsides with the onset of quiescence. This parallelism persists whether the stomach is in the fasting condition, or under the functionally stimulating influence of food.

In view of these findings and since ephedrine enjoys such a wide usage in medicine it was thought worth while to study its effects on the secretion of acid by the normal human stomach after an Ewald meal.

METHOD

Three healthy young male subjects were used in this work. The normal gastric acidity curves in response to an Ewald meal were determined according to the fractional method.

No food had been taken since the evening before. At 8:00 a. m. the residuum was removed from the stomach by a Rehfuss tube and examined for pus,

TABLE I

The effect of ephedrine on the secretion of acid by the human stomach

Time in Minutes	Gastric Acidity in c.c. of 0.1 N NaOH per 100 c.c.			
	Normal		Ephedrine	
	Free	Total	Free	Total
0	0.0	0.0	0.0	0.0
15	12.7	34 4	10.9	32.8
30	26.1	56 8	22.2	54.2
45	38.2	72.0	26.4	64.9
60	49.7	82.6	30.8	70.0
75	56.1	87.6	34.7	74.1
90	57.3	88.8	38.7	76.2
105	53.9	82.6	42.8	76 9
120	46.2	71.7	41.0	72.5
135	37.1	59.1	41.4	68.2
150			42.5	70.5
165			37 1	64.3
180			30.6	63.9

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Submitted April 17, 1937.

distinctly decreased both the total acidity and the free hydrochloric acid of the gastric juice.

In view of these findings, combined with the well established fact that ephedrine in therapeutic doses depresses gastric motility, it is suggested that this drug might find therapeutic application in the treatment of certain selected cases of uncomplicated gastric ulcer.

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Vitamin C Nutrition in Pulmonary Tuberculosis*

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THE literature relating to experimental animals indicates a decreased resistance to tuberculous infection in animals on a vitamin C deficient diet (1-8). Mouriquand and co-workers (5), Bieling (6), Heymann (3) and Basu (7) showed that the combination of a partial depletion of vitamin C and progressive tuberculous infection shortened the life of guinea pigs. Greene and co-workers (8) demonstrated clearly the effect of vitamin C deficiency on tuberculosis in guinea pigs. They conclude: "Chronic vitamin C deficiency combined with a progressive tuberculous infection causes a significant shortening of the survival period and a significant decrease in the body weight of guinea pigs." Beiling (4) found that animals with chronic tuberculosis were more easily precipitated into acute scurvy.

The literature dealing with hypervitaminosis C in animal tuberculosis is inconclusive. Leichtentritt (9) gave large amounts of orange juice to tuberculous guinea pigs on normal diets and found the survival period to be twice as long as that of tuberculous animals on the normal diet. Grant (10) reported that increasing the amount of vitamin C seemed to decrease the severity and extent of the tuberculous lesions in the lungs of guinea pigs. Bella (11) noted no increased resistance in tuberculous animals whose diet was supplemented by orange juice and cevitamic acid. Heise and Martin (12) found no protection from the use of cevitamic acid given intravenously over a period of five months. The question of hypervitaminosis C in tuberculosis of experimental animals is by no means settled.

Results obtained from experiments on animals cannot be expected to apply also to human tuberculosis as it is a well known fact that a disease analogous to human tuberculosis has never been produced in experimental animals. Clinical reports (1, 13, 14, 15) have appeared to the effect that scurvy renders a patient increasingly susceptible to tuberculosis, while the addition of vitamin C to the diet improves the prognosis in these cases. Schroeder (16) has reported increased requirement of vitamin C in all diseases accompanied by fever. Three cases of tuberculosis were studied: two for a period of five days during which they were fed 300 mg. of ascorbic acid daily. The report of Bullowa et al (17) shows in one tuberculous patient a reduced excretion of vitamin C but with prolonged dosage of ascorbic acid a high peak was reached which fell rapidly on discontinuing the treatment.

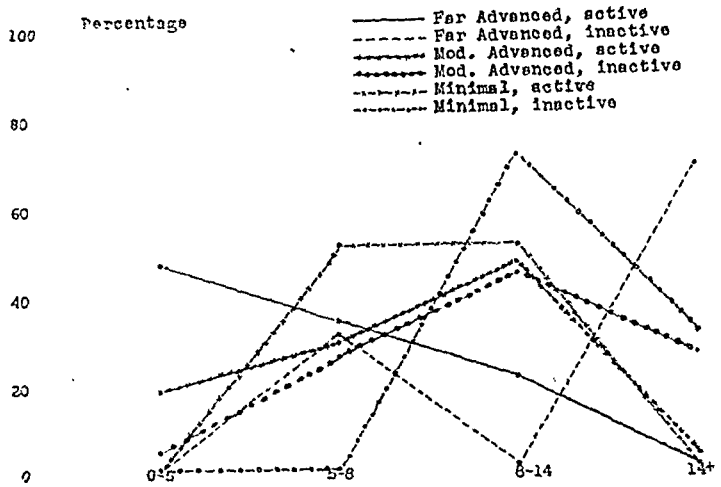
PROCEDURE

One hundred fifty tuberculous patients and fifteen normal non-tuberculous individuals were studied. The state of vitamin C nutrition was determined by collecting 24-hour urine samples, using glacial acetic acid as a preservative, and titrating with 2-6 dichlorophenolindophenol. Tillmanns and associates (18, 19, 20), Harris and associates (21), and Bessey and King (22) have demonstrated the close correlation between vitamin C biological assays and the titration values, using this indicator. All patients and controls were on the regular sanatorium diet. This permits of comparison of individual cases, but the results cannot be compared with those of other workers dealing with uncontrolled basic diet. The test dose method of determining the state of subnutrition as described by Abbasy et al (23) was used in many cases. The test dose of ascorbic acid* was given intravenously in some instances and orally in others, both normal and tuberculous individuals being tested. The extent and activity of the tuberculous process was simultaneously determined by X-ray, sputum examination, sedimentation rates and in some instances by tuberculin skin tests. It is to be emphasized that this study deals with uncomplicated tuberculosis. Exceptions to this will be designated. Any attempt to correlate extent and activity of tuberculous involvement with vitamin C nutrition would be futile in the presence of any complicating diseases. This factor was eliminated in this study by constant observation and routine physical examinations. Evidence of the effect of other diseases on the state of ascorbic acid metabolism is discussed

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*All ascorbic acid supplied by Merck & Co., Rahway, New Jersey.



Graph 1. 24 hour ascorbic acid excretion in pulmonary tuberculosis, subdivided into four excretion levels.

in reviews (23, 24, 25) and is too extensive for discussion here. Urinary pH was checked in all cases, as Hawley et al (26) have shown that alterations in urinary pH have a definite effect on the vitamin C content of the urine. The amount found was less when the reaction was alkaline. Variations in pH were within 1, which eliminates pH as a complicating factor in this work. Selection of cases was made to include inactive and active cases classified as minimal, moderately advanced and far advanced.

The 2-6 dichlorophenol indophenol was standardized every third day against pure crystalline ascorbic acid. Microburettes were used in the titrations. All ascorbic acid given intravenously was the neutralized product.

RESULTS

Excretion of Ascorbic Acid on the Sanatorium Diet; no supplements.

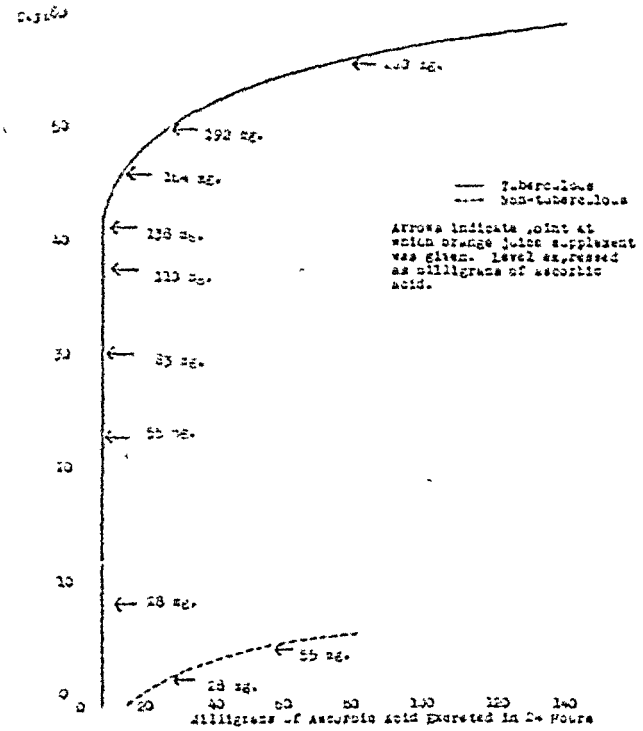
In a study of 116 cases, Table I, 10 normal (non-tuberculous) cases were found to be excreting 14 mg. of ascorbic acid or more daily. Those with tuberculosis fell into four principal groups: (1) in which the daily excretion ranged from 0 to 5 mg.; (2) in which the daily excretion ranged from 5 to 8 mg.; (3) in which the daily excretion ranged from 8 to 14 mg.; (4) and the group in which the daily excretion was 14 mg. or more. Sixteen out of 106 tuberculous cases showed an excretion of over 14 mg. of ascorbic acid in 24 hours. The range here was from 14 to 18 mg., whereas the non-tuberculous control group showed a range from 17 to 44 mg. daily on the same diet. A series of twenty cases was studied to determine the general effect of the sanatorium diet on vitamin C excretion. A determination of ascorbic acid was made when the patient was admitted and again two weeks later. As all twenty of these cases showed, on the second determination, slight increases of from 1 to 3 mg. daily in their vitamin excretion, values for comparison recorded in this paper are exclusively values determined after the patients had been on the sanatorium diet over two weeks. Fifty-four cases judged active by clinical and laboratory findings were studied: 22 of these excreted above 8 mg. of ascorbic acid daily; 1 case excreted above 14 mg. daily. Fifty-two cases judged inactive by the same criteria were studied: 13 of these excreted less than 8 mg. of ascorbic acid daily, and 2 excreted below 5 mg. of ascorbic acid daily. Generally, all cases of pulmonary tuberculosis have a hypovitaminosis C as a complicating factor, and the degree of this hypovitaminosis seems to parallel roughly the extent and activity of tuberculous involvement.

Ten cases of pulmonary tuberculosis with intestinal involvement were studied but failed to show any

TABLE I

Acorbic acid excretion and extent and activity of tuberculous Involvement. Number of cases in each group

Daily Excretion	Non-Tuberculous	Minimal		Moderately Advanced		Far Advanced		Total
		Inactive	Active	Inactive	Active	Inactive	Active	
0-5 mg.	0	0	0	2	7	0	7	16
5-8 mg.	0	0	1	10	12	1	5	29
8-14 mg.	0	7	1	17	17	0	3	45
14 or more mg.	10	3	0	10	1	2	0	26
Total	10	10	2	39	37	3	15	Total Cases 116



Graph 2. The daily ascorbic acid excretion of tuberculous patients on varying levels of orange juice. Curves represent average values for five tuberculous patients and two non-tuberculous cases.

feature of ascorbic acid nutrition distinguishing them from patients with no intestinal tuberculosis.

The ascorbic acid excretion of the entire group, 116 cases, was determined on at least two occasions and in some instances followed for five months, determinations being made at biweekly intervals. Determinations made at biweekly intervals on the same patients were found to check within 1 or 2 mg. in 95% of cases. In the ten patients studied over a period of five months, improvement was accompanied by an increased excretion of ascorbic acid. In two of these cases, a sudden decrease in ascorbic acid excretion was noted and when checked by a roentgenological examination both cases were found to have suffered an extention of pulmonary disease and a flare-up in activity.

One hundred thirteen patients were classified in three groups according to the roentgenological findings immediately after determination of the ascorbic acid excretion. First, those whose lesions appeared stationary, of whom there were 46; second, those whose lesions progressed, of whom there were 10; and third, those whose lesions improved, of whom there were 57. In the stationary and improved groups, the majority fell in the groups excreting 8 mg. or more daily,

TABLE II

Classification of cases as stationary, improved or retrogressive; subdivided according to ascorbic acid excretion

Ascorbic Acid Excretion, 24 hr. Period	Improved	Stationary	Retrogressive
0-5 mg.	3	5	5
5-8 mg.	15	15	3
8-14 mg.	26	16	2
14 mg. or more	13	10	0
Total Number of Cases	57	46	10

whereas 80% of those whose lesions progressed fell into the groups excreting less than 8 mg. daily. None of those whose lesions progressed fell in the normal group for excretion, whereas 22% of those whose lesions remained stationary were in the group where excretion was 14 mg. or more, and 22% of the improved group had an excretion of 14 mg. or more. Table II clearly shows the parallelism of condition of patients as determined by roentgenological findings and results of ascorbic acid excretion tests.

One hundred patients were classified according to the occurrence of positive or negative sputum at the time of determination of the excretion, and there appeared to be no relation between the quantitative excretion of ascorbic acid and the occurrence of tubercle bacilli in the sputum.

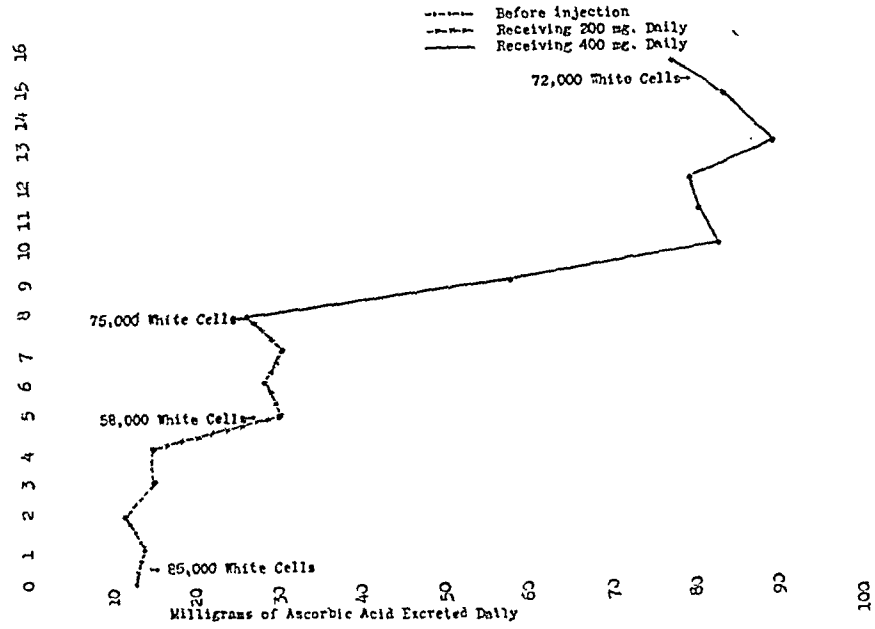
Using the Cutler method, the blood sedimentation rate was determined in 74 patients of whom 51 were males and 23 females. Twenty-seven of the males had a normal sedimentation and 24 an increased sedimentation rate. 37% of those with a normal sedimentation rate likewise had an excretion of 14 mg. or more per day, whereas only 12% of those with high sedimentation rate fell into this group. On the other hand, of those with high sedimentation rate, almost 30% fell in the low excretion group of 0-5 mg., whereas only 4% of those with normal sedimentation rates fell in this group. Of the 23 females, 6 had normal and 17 high

TABLE III

Response of tuberculous patients to a 1 ounce supplement of orange juice (55.2 mg. ascorbic acid) given daily over a period of 2 weeks. A positive response indicates saturation with vitamin C with increased urinary excretion

Condition	Number of Subjects	Minimal		Moderately Advanced		Far Advanced	
		Active	Inactive	Active	Inactive	Active	Inactive
Responses							
Total Number of Cases		2	8	10	15	4	
Percentage of each condition showing positive response		100	0	90	73	100	

sedimentation rates. Of those with normal sedimentation rates, 17% had a normal excretion of 14 mg. or more daily, and 50% fell in the groups 0-8 mg. daily. Of those with a high sedimentation rate, none fell in the extremely low (0-5 mg.) excretion group; 29% were in groups of 8 mg. or less of daily excretion, and 12% had a normal excretion of 14 mg. or more daily.



Graph 3. Ascorbic acid excertion in a patient with tuberculosis and myeloid leukemia following intravenous ascorbic acid.

Responses to Supplements of Vitamin C in Patients with Pulmonary Tuberculosis.

Forty-one patients and eight non-tuberculous individuals were given four ounces of orange juice (55.2 mg. of ascorbic acid by titration) daily for two weeks to determine if possible the saturation point. Twenty-one became saturated and 20 remained unsaturated. The eight non-tuberculous persons originally in the 14 mg. or higher group all gave a positive response. Eight patients were originally in the low group of 0-5 mg. excretion daily. Of these, one became saturated and seven did not become saturated. Fifteen were originally in the 5-8 mg. group. Of these, 46% became saturated and 54% did not. Seventeen were in the group of 8-14 mg. excretion daily. Of these, twelve became saturated and five did not. One was originally in the 14 mg. or more group and became saturated. Approximately 50% of patients became saturated after the use of supplements of 4 ounces of orange juice. Of fifteen active cases, only one became saturated, whereas of 26 inactive cases, 20 became saturated. This checks closely with roentgenological findings. The patients who gave no response to a four-ounce supplement of orange juice daily were continued on varying levels of orange juice to determine the daily intake of ascorbic acid necessary to cause it to saturate the body and spill over into the urine. Two non-tuberculous cases were given comparable doses as controls, although they responded to a 2 oz. supplement of orange juice. Table IV and Graph 1 show the required dosage for positive reaction. Patient No. 9268, with far advanced active pulmonary tuberculosis, gave no positive response even when given 220 mg. of ascorbic acid daily in the form of orange juice. The other patients gave positive responses eventually but only after huge dosages. Each dosage level was continued with each patient until no increase in urinary excretion was observed. In two cases a four ounce level of orange juice (55 mg. of ascorbic acid) was continued for four months with no response. This indicates definitely that it is not a matter of unsaturation solely but also of a marked increase in the daily destruction or utilization of ascorbic acid. The daily requirement of vitamin C for a tuberculous patient may safely be put at 110 mg. (about 8 ounces of orange juice). This provides a factor for safety. Negative results in attempts to saturate these patients might be attributed to one of two factors: alterations in intestinal chemistry (absorption mechanisms from the intestinal tract or destruction by bacteria in the intestinal tract) or increased demands for ascorbic acid by the tissues. Intravenous administration of ascorbic acid was next tried. This eliminates any factors of abnormality in the intestinal tract of the patient in pulmonary tuberculosis. Ten patients were given 200 mg. of cebione intravenously daily; seven of these responded positively, and three did not. All were roentgenologically classified as moderately advanced active cases of pulmonary tuberculosis. Comparison of response to a 200 mg. intravenous dosage and a 220 mg. oral dosage of ascorbic acid would indicate an abnormality in the intestinal tract causing destruction of or deficient absorption of ascorbic acid. Patient No. 9379 and Patient No. 9268 both showed a negative reaction to 220 mg. oral dosage of cevitamic acid given over a period of 6 days and 14 days respectively. The presence of patients showing a negative response to intravenous therapy made it imperative to select a level for intravenous dosages which gave no positive

responses when taken orally. As shown in Table IV no positive reaction was noted to the oral administration of 55 mg. of ascorbic acid and therefore 50 mg. was selected as the intravenous dosage. Four patients were tested; each being given 50 mg. of ascorbic acid daily by the intravenous route. Three of these gave a positive reaction excreting on the fifth day over 35 mg. of ascorbic acid; the fourth patient failing to respond. This evidence leads us to believe that two factors are responsible for the subnutrition observed in tuberculars; an increased demand by the tissues and a deficient absorption.

TABLE IV

Ascorbic acid excretion of patients on varying levels of orange juice. (Moderately or far advanced cases)

Level Expressed as Mg. of Ascorbic Acid Daily	Case Numbers with Daily Excretion In Milligrams										
	N T	9379 MAn	9357 MAı	9419 MAn	9482 MAn	9417 MAn	9522 MAn	9402 A MAı	9473 A MAn	9268 FAn	9454 MAn
0	18	4	8	6	7	4	—	—	7	4	5
28	30	10	7	9	8	8	—	—	8	7	6
55	60	5	10	9	10	17	6	—	10	8	7
83	70	4	28	18	10	17	8	7	14	8	10
110	101	6	—	38	16	14	28	34	46	9	12
138	—	10	—	—	30	32	72	8	—	8	7
164	—	—	48	—	—	—	—	—	—	10	10
192	—	10	—	—	—	—	—	—	—	12	140
220	195	28	—	—	—	—	—	—	—	12	—
251	—	175	—	—	—	—	—	—	—	—	—

Patients maintained on each level until no further increase in daily ascorbic acid excretion.

One patient under observation with a minimal case of tuberculosis was found to be suffering from myeloid luekemia. To study both the effect on his tuberculosis and on the leukemia, intravenous ascorbic acid therapy was begun A weak positive response was elicited; 30 mg. of ascorbic acid being excreted on 4 days following a 200 mg. intravenous dose. When the dose was raised to 400 mg. daily, the excretion rose to around 80 or 90 mg. daily. The ascorbic acid had no effect on the white count: the original value before treatment was 72,000 and the final value after the injection of 4200 mg. of ascorbic acid was 85,000, as shown in Graph 2. Eufinger and Gaehtgens (27) have reported the treatment of a case of myeloid leukemia in which the white count was brought back to normal and the clinical picture improved by the injection of 2000 mg. of ascorbic acid. It is difficult to explain the discrepancy.

DISCUSSION

No adequately controlled evidence on the effect of ascorbic acid therapy on the course of pulmonary tuberculosis was obtained in this study. The impression gained from the study is that it does improve the prognosis, but no definite evidence for this impression was obtained. Bachstrom in 1734 (Observationes circa scorbutum) noted a relationship of tuberculosis and vitamin C nutrition. He stated that scurvy could be cured by fresh vegetables provided tuberculosis was not a complicating factor. The relationship has been assumed but not definitely established. All reports to date showing favorable effects on prognosis in tuberculosis of vitamin C have been entirely inadequate to prove the contention. A statistical analysis of these papers would clearly demonstrate their inadequacy.

The present study demonstrates the existence of a hypovitaminosis C in a large majority of tuberculous patients; the degree of hypovitaminosis is shown to parallel the extent and activity of the tuberculous process.

The demonstration of the intestinal tract of the tuberculous patient as a factor in this subnutrition would indicate a loss in the specific absorptive powers of the normal gut for ascorbic acid. The intestinal flora might play a part. Stepp and Schroeder (28) have demonstrated a relation of C hypovitaminosis to the bacterial flora of the gut. Strains of bacillus coli and paratyphus B cause almost total destruction of vitamin C in the intestinal tract The tubercle bacillus might act in a similar manner and its presence in varying numbers in the intestinal tract of the tuberculous patient is certain. The extent of swallowing of bacilli laden sputum would be proportional to extent and activity of the disease; a fact in harmony with the parallelism shown in the degree of C hypovitaminosis and in the extent and activity of the disease. Schroeder and Einhauser (29) have suggested three types of hypovitaminosis C: first, due to a lack of vitamin C in the diet; second, due to deficient absorption caused by altered chemistry of the intestinal tract or bacteria; and third, due to increased requirements of vitamin C. The increased pigmentation seen in certain cases of far advanced tuberculosis is another indication of C deficiency.

The successful treatment of certain hemorrhagic diseases by ascorbic acid has led to the treatment of hemorrhage in tuberculosis with vitamin C. Hasselbach (30) reported results of the treatment of 8 cases of hemorrhage from tuberculosis; two did not respond. Cotti and Larizza (31) attribute the decrease in coagulation time caused by ascorbic acid injections to an increase in coagulation ferments. Junghaus (32) used ascorbic acid with success in the treatment of gynecological bleeding. Two reviews (24, 25) adequately cover the papers dealing with the use of

vitamin C in the treatment of hemorrhagic disorders. Our attempts to stop hemorrhage in tuberculosis by the intravenous administration of ascorbic acid were not successful. Eight attempts gave no positive results. Judging from previous experience the conclusion was reached that the period over which the pulmonary hemorrhage extended was in many cases shortened; however, a larger series would be necessary to establish this point. That immune mechanisms are impaired by deficient vitamin C nutrition has been established by Jusatz (33). Dogs on a vitamin C free diet were shown to have a low bacteriacidal power of blood. The precipitin titer was 100X greater after the injection of ascorbic acid into the vitamin C free animals. That the mechanisms of immunity are materially altered by ascorbic acid therapy in tuberculosis is shown by the work of Heise, Martin and Schwartz (34) who observed decreased sensitivity to tuberculin following injection of the vitamin.

Svirbely (35) reports that ascorbic acid in adequate amounts is necessary for the proper utilization of the cortical hormone. His findings apply particularly to the localized concentration of ascorbic acid in the adrenal itself. Tislowitz (36) stresses the relationship of cortical function and vitamin C nutrition. Siwe (37) noted a marked C hypovitaminosis in Addison's disease. These reports in combination with the observations of Siehrs and Miller (38) that vitamin C disappears from the adrenals in 3-6 days (long before symptoms of scurvy develop) leads one to believe that an inadequacy of ascorbic acid might be causing abnormalities in hormone function. Adrenal involvement has long been suggested as a complicating factor in tuberculosis and it would seem that the hypovitaminosis C plays an important part. Four cases of advanced pulmonary tuberculosis (39) treated with cortin (donated by Dr. E. C. Kendall) showed no response; but this does not rule out a possible effect, as ascorbic acid therapy was not instituted at the same time. These patients were far advanced cases of long standing and perhaps not the best patients for a trial. Attempts to study the effect in minimal cases would require large numbers of patients and enormous quantities of the cortical hormone.

It is a well known fact that tuberculous processes in the lung are walled off by fibrous connective tissue. Healing of the tuberculous process is a process of fibrosis. Failure to build up a protective wall around the tubercle is conductive to spreading of the disease. That vitamin C is required for the maintenance of all connective tissues is also well known. Fibroblasts, osteoblasts and odontoblasts undergo atrophy; and their inter-cellular fibroglia and collagin fibrils become degenerate, edematous and hyalinize. Considering these facts, the necessity of maintenance of optimal vitamin C nutrition in tuberculosis is obvious. Ascorbic acid applications have been used successfully to stimulate the formation of granulation tissue and hasten healing of surgical wounds (40). It would seem that in any disease accompanied by fever there is an increased demand for vitamin C; in tuberculosis it is doubly essential to promote fibrosis. Excretion of ascorbic acid, the degree of hypovitaminosis C, is not specific for any one disease. This is demonstrated clearly by the work of Drigalski (41).

It is to be emphasized that this work deals with uncomplicated tuberculosis. Hypovitaminosis C is no more characteristic of tuberculosis than it is of other chronic and many acute diseases. The value of ascorbic acid excretion determinations in the prognosis of tuberculosis rests on the absence of complicating diseases. It is suggested that patients with tuberculosis have a polyhypovitaminosis; and although difficult methods of determining degree of hypovitaminosis have prevented work with the other vitamins, this will doubtless be found true when clinically applicable procedures are developed. The nutritional defect in tuberculosis is multiple but the predominating deficiency is the hypovitaminosis C. The importance of an ample diet has long been recognized as an adjunct to the rest cure of tuberculosis and its importance doubtless lies in increased requirement of tuberculous individuals for all the vitamins. Multiple nutritional deficiency again cannot be claimed as specific of tuberculosis; all chronic diseases and many acute diseases with fever would also show a multiple nutritional deficiency.

TABLE V

Excretion of ascorbic acid by tuberculous patients following the intravenous administration of 200 mg. daily

Days	Excretion in Milligrams													
	1	2	3	4	5	6	7	8	9	10	11	NT	NT	NT
0	6.03	11.6	8.9	8.4	3.4	5.2	6.1	8.2	42.6	4.9	5.1	17	24.0	15.4
1	76.3	107	23.6	72.0	22.0	21.2	8.0	8.3	119.0	7.2	6.4	107	95.0	84.5
2	113.0	112.0	15.5	118	69.5	41.0	27.4	22.7	180.0	12.7	10.0	155	183	145
3	—	78	12.6	109.2	94.3	68.5	17.3	13.2	174	—	11.1	—	—	—
4	—	101	11.4	94.5	92.0	77.0	16.4	33.7	161	12.4	13.0	—	—	—

SUMMARY

Hypovitaminosis C is the rule among patients with pulmonary tuberculosis. The degree of hypovitaminosis parallels the extent and activity of tuberculous involvement. Two factors were demonstrated as responsible for the hypovitaminosis; first, abnormal chemistry of the intestinal tract, and second, increased requirements by the tissues of vitamin C.

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Gastro-Intestinal Symptoms from Cardiovascular Disease*

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GASTRO-INTESTINAL symptoms may arise from sources outside of the alimentary tract. They may arise from causes within the cardiovascular system.

Abdominal distress is merely an expression of trouble somewhere in the body. It is not an index of the location of the lesion producing the symptoms. The abdomen has been properly called the barometer or the spokesman of the body. It merely tells of trouble. It remains for the physician to locate the trouble, bearing in mind that the responsible organ may be located anywhere in the body.

Elsewhere we have pointed out that gastro-intestinal symptoms may originate in the renal system (1) and within the pelvis (2). It is the purpose of this paper to discuss the relationship of the cardiovascular system to the abdominal symptoms.

There are four cardiovascular diseases that sometimes produce pronounced gastro-intestinal symptoms; namely, coronary disease, congestive heart failure, endocarditis, and arteriosclerosis. The mechanism of the production of the abdominal symptoms is different in each of these disease groups, although the resulting clinical syndromes may resemble each other.

CORONARY DISEASE

Coronary disease produces gastro-intestinal symptoms by reflex mechanism acting through the autonomic and vagus nerves. There are no gross lesions present in the gastro-intestinal tract to explain the symptoms that occur.

The clinical picture that coronary thrombosis produces in the abdomen is extremely variable. It varies from a vague abdominal distress continued over a period of months, to a sudden attack of violent pain simulating a ruptured abdominal viscus.

Coronary disease may mimic any type of acute disease in the upper abdomen, although commonly it tends to produce a symptom-complex that resembles gall bladder disease. In 1928, Riesman (3) pointed out that acute coronary obstruction may simulate biliary colic, perforation of a peptic ulcer, acute pancreatitis, or intestinal obstruction; while a nonobliterative endarteritis is also capable of producing digestive symptoms but in a milder degree. In the latter type of case the outstanding symptoms are fatigability on slight exertion, shortness of breath, a sense of oppression in the precordial region or in the epigastrium, and frequently distension with gas. It is the last symptom that often dominates the clinical picture and gives the impression of a primary gastric disease. Riesman however cautions that it is possible for both digestive and myocardial disease to be present at the same time.

Katzman (4) has pointed out that the abdominal symptom-complex resulting from coronary thrombosis is commonly considered by the laity to be a form of acute indigestion, and that the majority of deaths reported in the newspapers as "acute indigestion" are really cases of coronary thrombosis.

Coronary thrombosis may mimic biliary colic so closely, that it requires careful analysis to differentiate the two conditions. In considering the differential diagnosis between these diseases, the following signs and symptoms are mentioned as diagnostic of biliary colic: severe pain in the right upper quadrant of the abdomen which may radiate to the back, nausea and vomiting, jaundice, a slight elevation of the temperature, a slow or a normal pulse rate, the heart tones remain strong, there is no pericardial friction rub, there are no characteristic alterations in the electrocardiographic tracing from day to day; whereas in coronary thrombosis the following signs and symptoms may be present: severe pain in the upper abdomen accompanied by considerable shock, the pain does not radiate to the back, it may, however, radiate to the epigastrium or to the substernal region, it is crampy and paroxysmal, there is marked dyspnoea, nausea and vomiting may occur, jaundice is rare, there is some elevation of the temperature, the pulse becomes rapid, the heart tones are distant, a pericardial friction rub may be present or may develop, the blood pressure

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drops from 20 to 50 mm., the electrocardiographic tracing may show a high take-off of the T wave as well as a cove shaped inversion, also there may be a sudden shift of the electrical axis, furthermore there may occur a variation in the electrocardiographic tracing from day to day with a gradual falling of the high take-off of the T wave, the attack usually follows a combination of severe mental anxiety and excessive physical effort on part of the patient, although several hours may elapse between the physical strain and the coronary attack.

In addition to those cases of coronary disease where the onset is sudden and dramatic, there are other cases where the symptoms are less violent, where the onset is gradual, where the course is milder, and where the differential diagnosis is much more difficult to make.

Obviously not all cases of coronary disease effect a dramatic onset either thoracic or abdominal. Common sense dictates that for every case of coronary disease that terminates in a thrombosis, there must be many more cases that remain in the nonobliterative stage; also there are those cases where the process of thrombosis and infarction is quite slow in developing; consequently there must be many more patients with mild coronary symptoms than patients with drastic symptoms.

White (5) has pointed out that coronary disease occurs in a large percentage of patients with heart ailments. He states that in a study made in New England, 37 per cent of a series of 2,314 patients with organic heart disease were found to have some degree of coronary involvement. White considers that infarct-producing and clinically recognizable coronary thrombosis is but a single phase of coronary disease, although a striking one.

In the nonobliterative type of coronary disease, the abdominal symptoms do not always present clear cut syndromes. Often they may be vague, or they may mimic any of the common types of gastro-intestinal disorders, while at other times they conform to no known type of gastro-intestinal syndrome. When the patient presents this stage of the disease, it may be quite difficult to differentiate the mild coronary syndrome from the gall bladder dyspepsia. However the *clinical* course of the patient sometimes suggests the possibility of the underlying cause being located elsewhere than in the gastro-intestinal tract, when the patient fails to respond to gall bladder therapy.

Another type of overlapping of coronary and digestive symptoms occurs where there are signs and symptoms pointing to both diseases. Thus a patient complains of fulness in the epigastrium after meals, attacks of pain in the gall bladder region which radiate to the scapula, periods of mild jaundice and clay colored stools, and then subsequently develops precordial pain, cyanosis and shock. In this instance there is likely to be present both diseases. There is nothing unusual in the thought that both diseases may coexist in the same individual. On the contrary it is to be anticipated, since both diseases occur in the same age groups as well as in the same type of constitutional habitus.

In discussing the differential diagnosis between coronary and gall bladder disease, we have not stressed the use of the gall bladder dye test. In a few instances where we have seen the dye test made in the presence of coronary disease, there occurred such violent reactions after the ingestion of the dye, that we have discontinued the dye test in the cases of possible coronary involvement.

The following case reports illustrate some instances of digestive syndromes which apparently originated in the coronary arteries.

Case I. Gall Bladder Dyspepsia Syndrome from Coronary Thrombosis with Recovery.

D. F. H., a physician, 45 years old, 5 feet 10 inches in height, weighing 170 pounds, is a veteran of the world war. He believes and practices the out door life. He is a golfer and a mountaineer. He has always prided himself in his splendid physical condition. He believes that at his age he can play 36 holes of golf or climb a mountain with the vigor of his youth.

D. F. H. began to develop vague abdominal symptoms. At first he noticed a fulness after meals, later he was annoyed with belching and flatulence, then he developed spastic constipation. He had been working hard and worrying over an economic situation over which he had no control. He thought that he was growing flabby, so he increased his physical exercise. The digestive symptoms, however, did not subside. On the contrary they were becoming more annoying. The epigastric fulness after meals grew very distressing, necessitating the loosening of his clothing. He considered the symptoms the result of a gall bladder dyspepsia and accordingly placed himself on a restricted diet and bile salts with pancreatin therapy. However he did not improve. He grew steadily worse for several months, also he noticed increased fatigability and some shortness of breath. He continued with his program of physical exercise. One Sunday afternoon while climbing over his favorite mountain he found a large sized rock that he thought would add to the appearance of his rock garden. He proceeded to haul it on his shoulders to his car. He retired early that evening because of fatigue. At 6 a. m. the following morning, he was suddenly awakened with a terrific agonizing attack of pain under the sternum. He had a horrible sensation of choking and inability to catch his breath. A sensation of impending death oppressed him. The pain radiated down both arms. The agonizing pain continued for about half an hour and then gradually subsided.

When seen several hours later he was ashen-white in color, an obviously sick man. The heart was slightly enlarged, the mitral first sound was weak and indistinct. The blood pressure was 110-55, a fall of 25 mm. from a recent test. The pulse was rapid with a rate of 110 per minute, the temperature was 99.4. There were no abdominal signs or symptoms at this time. An electrographic tracing shows inverted T waves of the Pardee type in lead I.

A diagnosis was made of Coronary Thrombosis.

The patient was put to bed for six weeks. He was placed on a maintenance diet and given theobromine gr. 5 and phenolbarbital gr. ½ after meals. After the first day he became free from symptoms. At the end of six weeks, he was placed on a controlled program of exercise and subsequently returned to his practice.

Comment. Patient D. F. H. presented a digestive syndrome as an expression of coronary disease. The coronary disease probably resulted from the combined physical and mental stress in a high tension individual. The patient continued to have digestive symptoms as long as the coronary disease was of the nonobliterative type. The symptoms imitated gall bladder dyspepsia. Treatment for the gall bladder dyspepsia did not relieve the symptoms. Later the patient developed a typical attack of coronary thrombosis and the diagnosis became evident. When the patient was placed on treatment for the coronary lesion, the digestive symptoms subsided.

Case II. Gall Bladder Disease Syndrome from Coronary Thrombosis with Recovery.

B. M., age 60, is a self made man, and a successful one. He "arrived" by hard work. At the age of 60 he is a successful banker and still works hard, too hard for a man of his age. For several years he has been under a mental strain by reason of rumors of inflation of the currency. Recently he had purchased a ranch where he had hoped to spend his declining years. He started to get acquainted with his ranch by pitching hay and chopping away some underbrush.

B. M. is 5 feet 2 inches in height and weighs 135 pounds. He has always enjoyed robust vigorous health. However, about November 2, he began to experience a disagreeable sensation under his right hypochondrium. Then the pain became sharp and boring, and radiated to the epigastrium. He also complained of fulness after meals, flatulence, gas eructations, some shortness of breath and some loss of strength. The syndrome pointed to a gall bladder dyspepsia, and arrangements were made to study the gall bladder roentgenologically. The patient, however, wished to delay the examination in order to make the necessary arrangements for absenting himself. On the evening of Nov. 12, he had a sudden attack of excruciating pain in the precordium which radiated down both arms.

When he was seen about an hour later he was still having the agonizing distress. He appeared cyanotic, cold, and clammy. His pulse was rapid, the mitral first sound was weak and distant. He had not taken the gall bladder dye. He was given a quarter grain of morphine, brought to the hospital, put to bed at absolute rest, and given theobromine gr. 5 and phenolbarbital gr. ½, three times daily and placed on a light diet. The next day his temperature was 101.4, the pulse 110, the respiration 20, the blood pressure 110/56 which was a decrease in the systolic pressure of 50 mm. from a week previously. The leucocyte count was 14,200. The electrocardiographic tracing shows inverted cove shaped T waves in lead III with a high take-off; in lead III there are also deep Q waves; in lead II there is a beginning inversion of the T waves.

A diagnosis of Coronary Thrombosis was made. The patient was kept in bed for six weeks, and then allowed to resume some of his activities slowly. After the second day in bed he became symptom free from both the thoracic as well as the abdominal symptoms.

Comment. Patient B. M. presented the syndrome of gall bladder dyspepsia as an expression of coronary disease. This continued for several days when a typical attack of coronary thrombosis appeared, which was confirmed by the electrocardiographic studies. The digestive symptoms subsided under treatment for the coronary disease.

Case III. Gall Bladder Disease Syndrome from Fatal Coronary Thrombosis.

A. G. was an attorney, a successful trial lawyer, one of those high-pressure dynamic personalities. He was trying a case in the district court that had attracted considerable attention. The case had reached the stage where on the following day he would make his final plea to the jury. If the jury rendered a favorable verdict for his client, the case meant much to him.

A. G. was a big strapping fellow of 50 years, he was 5 feet 11 inches in height and weighed 210 pounds. He had married recently and was greatly in love with his young wife.

On the morning of March 4, the day preceding his final plea to the jury, he awoke feeling nervous and tired, and somewhat pale in color. He attributed these symptoms to his anxiety over the outcome of the trial. Later in the day, after lunch, he had an attack of "acute indigestion," a sudden sensation of distress in the epigastrium with fulness and distention. The pain was quite severe. He felt nauseated, vomited, and felt somewhat relieved, but still weak. He took several aspirin tablets, and the distress eased up some, sufficient to permit him to make his way to the physician's office.

The syndrome presented by the patient at the time suggested an attack of gall bladder disease, so the patient was advised to go to a hospital immediately for observation and treatment.

A. G., however, would not enter a hospital on that day. He had that important address to make to the jury on the following day. He wanted his physician to give him a little something to fix him up for the remainder of the trial, after which he might enter the hospital. The physician again urged him to enter a hospital immediately and postpone his trial, all to no avail. He left the physician's office, went home, and died suddenly several hours later.

A postmortem showed a coronary thrombosis of the left coronary artery, a left ventricular hypertrophy, some generalized arteriosclerosis. The gall bladder was normal.

Comment. Patient A. G. presented a syndrome of digestive symptoms suggestive of a gall bladder syndrome as an expression of coronary disease. He died several hours later from a coronary thrombosis, which was confirmed by postmortem examination.

Case IV. Fatal Coronary Thrombosis with Gall Stone Obstruction.

E. W. K., age 66, was a mining engineer, who plied his trade with a youthful vigor. He had hardly known a sick day in his life. He was one of those men who had little use for "sissies," and had no time to be sick himself.

On Feb. 1, he was inspecting a mine up in Cripple Creek at an elevation of 10,000 feet. That noon he ate a heavy meal which contained excessive grease; about a half hour later he had an attack of "acute indigestion," with severe pain in the right hypochondrium and epigastrium. The pain radiated to the back. At first the pain was slight, then it grew steadily worse. The pain spread to the precordium and down both arms. He felt a sense of pressure about the heart, and he became short of breath.

There was no physician conveniently accessible at the time, so he sought relief by taking some soda, and felt better for a few minutes. Then the pain returned and with it he felt nauseated, so he took some ipecac, vomited, and felt considerably relieved. His temperature was taken by a mine superintendent and found to be 97, his pulse was 40. Mining men have a fear of contracting pneumonia in the higher altitudes, so he decided to get to a lower altitude as quickly as possible. The next day he came to Denver and was examined on Monday, Feb. 2. He recalled that he had been slightly jaundiced for several days, and that his stools had been clay colored.

Examination showed a well nourished man weighing 180 pounds, measuring 5 feet 10 inches in height. He was markedly dyspnoeic and short of breath, the temperature was 97 and the pulse was 55, the respiration was 20, the blood pressure was 116/62. The heart was slightly enlarged transversely, the mitral first sound was weak and distant. There was a definite tenderness in the gall bladder region, the lower border of the liver was palpable and tender. The urine contained bile, a trace of albumin, some casts. The white blood count was 15,200.

A diagnosis was made of Gall Stone Colic with Coronary Disease, and immediate hospitalization urged.

E. W. K. left the office to go to the hospital, but stopped at the hotel to gather up some luggage. While in his room, he had another attack of pain and died suddenly.

A postmortem examination showed a coronary thrombosis of the left coronary artery, generalized arteriosclerosis, left ventricular hypertrophy, a contracted thickened gall bladder containing some gall stones, a small stone in the common duct, jaundice, atherosclerosis of the aorta, etc.

Comment. Patient E. W. K. presented a syndrome pointing to both coronary disease and gall stone colic. A postmortem examination established the existence of both diseases.

CONGESTIVE HEART FAILURE

Congestive heart failure is a common cause of gastro-intestinal symptoms.

The mechanism of the production of symptoms is quite different from that in coronary thrombosis. Whereas coronary disease is considered to act on the gastro-intestinal tract by reflex mechanism through the autonomic and vagus nerves, or through the altered flow and resulting changes in nutrition, congestive heart failure produces organic changes in the abdominal viscera. These alterations in addition to the impaired nutrition resulting from the diminished blood flow are responsible for the abdominal symptoms.

The pathologic manifestations of congestive heart failure are extremely variable. The following lesions occur commonly: hypertrophy and dilation of the heart, coronary sclerosis, myocardial fibrosis, stasis of the portal circulation, stasis of the pulmonary circulation, and their diverse manifestations.

It is the portal stasis that is largely responsible for the digestive symptoms in congestive heart failure.

The rapidity of the development of the congestive heart failure determines the severity of the symptoms. Rapid engorgement of the liver may simulate acute disease of the upper abdomen, and may mimic acute gall bladder disease very closely. Wedd (7) has pointed out that in rapidly developing congestive heart failure, the liver acts as a reservoir for the blood, as a result of which it engorges rapidly. The hepatic capsule becomes suddenly distended, which results in acute pain in the upper abdomen, accompanied by distension, nausea and vomiting. This syndrome may mimic acute gall bladder disease, and had led to the performance of laparotomies that had better been left undone. He recites an instance where a laparotomy was performed for a supposed gall bladder disease, in which the gall bladder was found to be normal. Later it developed that the symptoms had been caused by engorgement of the liver due to congestive heart failure from auricular fibrillation.

The following case report illustrates a patient who presented pronounced gastro-intestinal symptoms from congestive failure due to mitral stenosis.

Case V. Acute Abdominal Pain from Congestive Heart Failure due to Mitral Stenosis.

Mrs. S. H., a housewife, complains of a sharp pain in the epigastrium which has persisted for three days. The pain appeared suddenly after the eating of a heavy meal. The pain has become constant. It is a boring, pressing pain, accompanied by a sensation of fulness and distension of the upper abdomen. The pain is aggravated by muscular effort. The patient also complains of considerable flatulence and constipation. There is some swelling of the ankles and some shortness of breath.

The writer saw this patient through the courtesy of Dr. Katzman of Denver.

Physical examination shows a well nourished woman, 56 years old, weighing 130 pounds and measuring 4 feet 10 inches in height. She is somewhat pale and dyspnoeic in appearance. The pulse rate is 96 per minute. The blood pressure is 150/90. The heart is enlarged 5 cm. to the left. A presystolic murmur is heard at the apex which is transmitted to the axilla.

The liver is enlarged and extends 8 cm. below the costal margin. It is palpable and tender. The muscles in the right upper quadrant of the abdomen are slightly tense and spastic. The abdomen is distended and tympanitic. The ankles are swollen. The bases of the lungs are dull and contain some moist rales.

A diagnosis was made of Mitral Stenosis and Congestive Heart Failure.

The patient was put to bed, given digitalis in adequate doses, and placed on a light diet.

Within a few days, the abdominal pain subsided, the liver receded, and the abdominal distention disappeared. The shortness of breath, however, continued for some time, but later it responded to continued treatment.

Comment. Patient S. H. presented a syndrome of acute abdominal pain, flatulence and abdominal distention as an expression of congestive heart failure due to mitral stenosis. The pain probably resulted from the sudden engorgement of the liver, which was found to be enlarged at the time of examination. When the patient was placed on treatment for the heart lesion, the digestive symptoms subsided.

ENDOCARDITIS

Like congestive heart failure, endocarditis causes digestive symptoms primarily by producing changes in the abdominal viscera.

The essential mechanism in the production of the symptoms consists in the formation of emboli which lodge in the spleen producing infarcts.

The spleen, next to the kidneys, is the commonest site of infarction from endocarditis either subacute or chronic. The resulting infarct is usually anemic in appearance, wedge shaped, yellowish white in color, bordered by an inflammatory zone. Multiple infarcts are common. Infarction of the entire spleen may occur. Nuzum (6) reports a case of massive infarction of the entire spleen due to an embolus from a mitral endocarditis which lodged in the splenic artery. The spleen was "a soft yellow necrotic mass not normal at any point."

The resulting symptoms are quite variable. They may be violent and simulate a ruptured viscus, the symptoms may be milder, or there may be a minimum of symptoms. Commonly there occurs a sharp attack of pain in the splenic region, accompanied by rigidity of the muscles in the left upper quadrant of the abdomen. At other times there is present a dull bearing down pain, and at other times no pain at all. The pain when present is aggravated by deep inspiration. Nausea and vomiting may occur. The spleen enlarges, becomes palpable and tender. A localized friction rub may appear which is an expression of a localized peritonitis. Fever occurs if the emboli contain bacteria which set up a local infection in the spleen which may then pass on to abscess formation. Nuzum states that vomiting of blood is of frequent occurrence; the blood may be bright or coffee ground in color.

The syndrome may simulate a ruptured abdominal viscus. This has been observed by Wedd (7) who states that "a primary cardiac disease which I have found to have significance for the surgeon is subacute bacterial endocarditis . . . . . Abdominal symptoms resulting from infarction of the spleen and perisplenitis occurring in subacute bacterial endocarditis have been observed, and three patients in whom laparotomies were performed have been recorded."

Infarction of the spleen may terminate fatally. This is apt to occur in subacute bacterial endocarditis

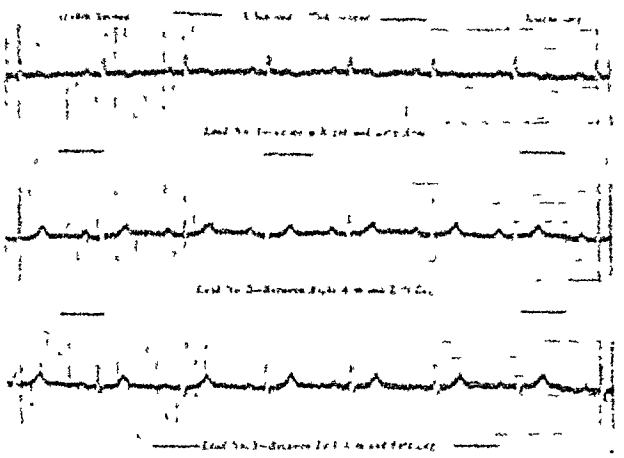


Fig. 1. Electrocardiographic tracing of patient D. F. H. having inverted T waves of the Pardee type in lead I.

where as a result of the bacterial emboli, the infarcts become infected. The infected infarcted area passes on to abscess formation, Peritonitis and death follow.

Vallee (8) reports such a case. His patient entered the Hotel Dieu Hospital of Quebec with cardiorenal disease. Examination showed evidence of both subacute bacterial endocarditis and chronic endocarditis of the mitral and aortic valves as well as renal insufficiency. The patient's course was without appreciable change from July to September when his temperature became elevated and irregular and he complained of acute pain in the left hypochondrium which he described as intolerable. The pain did not remain constant. It shifted to the right side, then disappeared, then reappeared again in the left upper quadrant with increasing severity. It continued in this shifting manner for four to five days, when the patient passed into coma and died. Postmortem examination showed peritonitis, chronic vegetative endocarditis of the aortic and mitral valves. The spleen was covered with a purulent exudate, and contained multiple infarcts, one of which was large, typically wedge shaped, pale in appearance and apparently several days old. The smaller infarcts were in various states of degeneration. There were multiple ruptures in the spleen, which Vallee believes resulted from a necrosis through the capsule as a result of the abscess formation which took place in the infected infarcts.

ARTERIOSCLEROSIS

Arteriosclerosis produces gastro-intestinal symptoms by causing organic changes in the abdominal blood vessels supplying the digestive tract.

Two stages of the resulting digestive syndrome occur, an early stage and a late one. In the early stage of the disease, the patient presents general dyspeptic symptoms as belching, flatulence, epigastric fullness after meals, constipation, heartburn, headache, biliousness. These symptoms are caused by an impaired functional activity of the digestive viscera due to a chronic bad blood supply and impaired nutrition, which compels the digestive viscera to work under stress.

At this stage, the digestive syndrome seldom imitates any abdominal disease. It is easily recognized for the functional disorder that it represents. It presents no problem in diagnosis. Therapeutically it usually responds satisfactorily to dietetic restriction, digestive and sedative therapy.

In the late stage of the syndrome, the patient develops attacks of violent pain in the abdomen. The pain is sharp and paroxysmal, sudden in appearance. It may locate anywhere in the abdomen, although commonly it centers in the epigastrium or the umbilical region.

At this stage, the syndrome may mimic gall bladder colic, renal colic, lead poisoning, tabetic crisis, or other types of acute abdominal disease. The underlying pathologic lesion for this sharp colicky pain is a marked sclerosis of the mesenteric arteries. These are markedly thickened, rigid, sclerotic, pipe-stem in character with diminished lumens.

This syndrome resulting from arteriosclerosis of the abdominal arteries supplying the digestive tract has also been designated as "angina abdominalis." Elsewhere (9) we have discussed this syndrome in detail. The term was introduced by Bacelli in 1897. The writer regards the term "angina abdominalis" as synonymous with the digestive syndrome occurring in cardiovascular disease resulting from a marked sclerosis of the abdominal arteries supplying the digestive tract.

The outstanding symptom is the pain. It occurs as a sharp paroxysmal pain, sudden in appearance, lasting from a few minutes to several hours, and it tends to occur two to three hours after the taking of food. It is commonly associated with general weakness, loss of weight, secondary anemia, distention, flatulence, biliousness. Our patients have described the pain as horribly severe and agonizing, the dread of which made their life a burden, and from which they would welcome permanent relief. Several patients required morphine for the relief of the pain.

Sometimes the pain becomes dull and continuous in character. The patient complains of a dull ache, soreness and sometimes a throbbing in the abdomen. At this stage the syndrome may simulate malignant disease of the abdomen.

Gilbride (10) has reported a series of four patients with arteriosclerosis who were suspected of having malignant disease by reason of their symptoms. In the case report (9) that the writer discussed under "Angina Abdominalis," patient L. B. M. had been sus-

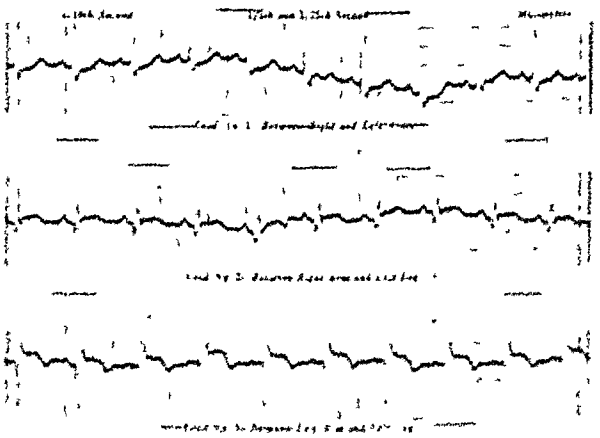


Fig. 2. Electrocardiographic tracing of patient B. M. showing inverted cove shaped T waves in lead III with a high takeoff, deep Q waves in lead III, and a beginning inversion of the T waves in lead II.

pected of having a carcinoma of the pancreas; and at one time had been admitted to a hospital with this diagnosis. The diagnosis of arteriosclerosis of the abdominal arteries supplying the digestive tract was subsequently confirmed by a postmortem examination. There was no malignancy present.

Regarding the nature of the abdominal pain in these patients, Ortner (11) believes that as a result of the marked arteriosclerosis of the mesenteric arteries, the intestines do not receive a sufficient quantity of blood, the intestinal walls become poorly nourished and are incompetent to perform their work efficiently. This becomes manifest several hours after the ingestion of food when the intestines take up their phase of the digestive cycle. Under the burden of this strained physiologic function due to the diminished blood supply, the visceral pain appears.

Regarding the question of whether it is possible for viscera to produce pain, Sir James MacKenzie (12) has stated that pain is a function peculiar to the cerebrospinal nervous system as distinct from the autonomic; nevertheless it is known that pain does arise from viscera. In this case the pain is referred to the distribution of the sensory nerves in the external wall and not to the viscera that initiate the impulses. There is only one demonstrable cause for visceral pain, and that is a contraction of muscle rendered anoxemic by insufficient blood supply. According to this view, an intestine which is engaged in its phase of the digestive cycle, will give rise to pain if its blood supply is deficient. Such is the case in marked arteriosclerosis of the mesenteric blood vessels, where the lumens of the vessels have been reduced in size.

Case VII. Gastro-intestinal Syndrome from Arteriosclerosis, so-called "Angina Abdominalis."

S. R., age 60, had been a retired merchant, and lived off the income of his real estate. He had enjoyed reasonably good health up to the time of the depression when he lost practically all of his property and was reduced to the necessity of living as a pensioner on a friend's bounty, when he began to fail in health and developed digestive symptoms.

He complained of abdominal pain after meals, coming on about two hours after the ingestion of food, also flatulence, belching, constipation, loss of weight, progressive weakness. In the past year he lost about fifteen pounds.

When he was first seen in August, 1934, his presenting symptom was abdominal pain. Although it had begun as a mild discomfort, it had increased in severity, so that he had sought relief from it. At first he obtained relief by lying down, restricting his diet, or taking soda. Later these had failed to give him relief. He restricted his diet still more, but still was unable to get the desired relief. He began to fear meal time, knowing the discomfort that followed.

S. R. was 5 feet 4 inches in height, weighed 135 pounds, he was pale and anemic in appearance, sallow in color. The blood pressure was 176/82. The heart was enlarged to the left, the aortic second sound was accentuated, the pulse was irregular with occasional dropped beats. The radial arteries were hardened and sclerotic. The eye grounds showed arteriosclerotic changes. An X-ray examination of the gastro-intestinal tract showed some spasticity of the colon with delayed emptying time. An Ewald test meal indicated a hypoacidity, the blood showed a secondary anemia. The stool was free from occult blood.

A diagnosis was made of Arteriosclerosis with Digestive Syndrome, so-called "Angina Abdominalis," Spastic Colon, Hypoacidity, Secondary Anemia.

The patient was placed under symptomatic treatment consisting of a maintenance diet given as frequent small meals, pancreatic extract with bile salts, theobromine with phenolbarbital and prescribed hours of rest. Nevertheless under treatment he continued to grow worse. The abdominal pain became sharp, paroxysmal and agonizing and required morphine for control. The patient lost weight, became emaciated, and developed a marked arrhythmia. The anemia increased, and he died following an attack of abdominal pain.

A postmortem examination showed generalized arteriosclerosis, some enlargement of the left ventricle, atherosclerosis of the aorta and coronary arteries. Of special interest were the mesenteric arteries which were hard, firm, brittle, sclerotic, pipe-stem in character with markedly reduced lumens.

SUMMARY

1. Gastro-intestinal symptoms may arise from lesions outside the gastro-intestinal tract.

2. They may arise from causes within the cardiovascular system.

3. There are four cardiovascular diseases that produce pronounced gastro-intestinal symptoms at times, namely: coronary disease, congestive heart failure, endocarditis, and arteriosclerosis.

4. Each of these four cardiovascular disease groups produces the abdominal symptoms in its own characteristic manner, although the resulting abdominal syndromes may resemble each other.

5. Coronary disease produces gastro-intestinal symptoms by reflex mechanism through the vagus and autonomic nerves, as well as through the altered blood flow and the resulting impaired nutrition.

Coronary disease sometimes simulates acute gall bladder disease. It is the fatal "acute indigestion" of newspaper accounts.

6. Congestive heart failure causes gastro-intestinal symptoms by producing organic changes in the abdominal viscera as hepatic engorgement and enlargement, portal stasis, etc. Sudden distention of the hepatic capsule is believed to account for the acute abdominal pain in congestive heart failure.

7. Endocarditis causes digestion syndromes by producing organic changes in the abdominal viscera. The essential mechanism consists in the formation of emboli which lodge in the spleen, producing infarcts.

8. Arteriosclerosis causes digestive symptoms by producing organic changes in the abdominal blood vessels supplying the digestive tract. The late stage of this syndrome has been designated as "Angina Abdominalis." It is characterized by a sharp agonizing paroxysmal pain coming on several hours after eating.

The mechanism of this pain is believed to be based on the impaired blood supply to the intestines due to diminution in the lumens of the mesenteric arteries. When the intestines are forced to labor under deficient blood supply, pain results.

9. Cardiovascular disease may mimic any type of acute abdominal disease although the following syndromes are commonly suggested: acute gall bladder disease, chronic gall bladder dyspepsia, ruptured abdominal viscus, renal colic, lead colic, and malignancy.

10. There are no pathogonomic gastro-intestinal symptoms of cardiovascular origin.

11. The differential diagnosis between cardiovascular and digestive disease is arrived at by a careful consideration of both systems aided by the electrocardiographic tracing of the heart which may show

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Von Bergmann does not frequently find diabetes due to overfeeding, as Joslin stresses with so much vigor. Yet he is also not inclined to look upon every obesity as an endogene one, and he finds transition forms from obesity due to overfeeding and laziness to the so-called endogene obesity. Von Bergmann does not think that obesity occurs with a special frequency in certain families and races, with which habits of food and cooking are hereditary, and he also contradicts the assumption that diabetes and obesity are linked together in many families in a hereditary-biological sense.

He places in the forefront, on the contrary, a special "lipomatous tendency," fastened to the tissue itself, and he attempts to show a hereditary disposition towards a disturbance of the carbohydrate metabolism, which, on the one hand, may lead to diabetes, on the other to obesity. This theory also may be acknowledged as a support for the necessity of prophylaxis of diabetes. V. Bergmann thinks that in the obese organism the way from carbohydrate glycogen to the transformation into fat may be made with more facility, and on the other hand the breakdown of the fat tissue by way of the ketone bodies is more difficult. It is also a characteristic feature of obesity that little glycogen is stored in the liver, the carbohydrate more easily flowing to the fat tissue, being gotten there more easily and converted into fat. Increased glycogenolysis, as found by the school of Bergmann besides diabetes in obesity too, is in no respect a diabetic metabolic disturbance. Such a disturbance of glycogen fixation is said to be able to lead to true diabetes. As long as the obese organism has the faculty to store the non-combusted amounts of carbohydrate in its fat tissue, so long is the second, the periphery factor of diabetes absent. If, however, it is no longer able to store the whole amount of carbohydrate, flowing to the fat tissue, it would yet transform only a part of it into fat. The remaining carbohydrate in this case would not be utilized any more. Glycogenolysis persisting, hyperglycemia and glycosuria must occur. In the obese person a true diabetes would become manifest.

The importance of the hereditary and the exogene factor are, consequently, quite differently appreciated by every investigator. None of them has any doubt that diabetes is a disease chiefly originating from a hereditary disposition. According to Umber, however, occurrence and character are fixed by hereditary disposition. The inheritance determines whether there is a mild or a severe form. Environmental influences are able to have some effect upon the course of the disease, not, however, upon its character. According to this view the power of heredity is the punctum saliens. In contrast to this rigid view, Joslin's opinion gains new followers, according to which exogene factors, in addition to the hereditary ones play an important rôle, among them chiefly obesity due to overfeeding.

While these very divergent views prevail there are also different views in regard to the possibility of an effective prophylaxis of diabetes. According to the view of the orthodox disciples of the Mendelian theory the recessive disposition is unavoidably transferred to the descendants. "According to the intensity of the hereditary disposition the manifestation of the disease occurs in an earlier or higher age" (Umber). The school of Joslin hopes to prevent the outbreak of the disease by favorable environmental influences. This conflict of views shows that we are still far removed from a deeper knowledge of the hereditary influences. We must keep in mind that it has not been possible hitherto to uncover the secrets of heredity. We therefore agree with Pannhorst that we are still in the dark about the hereditary factor itself, about the laws governing it and its dependencies, about its penetrance and its expressivity.

It would, however, be of great importance for the prophylaxis if it would be possible to influence the gene, the hypothetical carrier of the inheritance. But there is no hope of solving the problem of heredity by starting from the gene. Development is more than a chemical-physical process. Every natural variety has an "erbstock"—surrounded by changeable genes—braving every change and not being susceptible to any decisive influence by crossing or external measures. By external influence we are not able to root out a series of unwelcome qualities, summarized under the designation "hereditary taint" at best we can shift their manifestation. We cannot overcome our inheritance, and we must take into consideration the recessive hereditary disposition of diabetes. This experience restricts our prophylactic dealing regarding diabetes.

Nevertheless the prophylactic-therapeutical work in this disease must become more intense. The premise for a successful effort would be to recognize more frequently and at an earlier stage a diabetic disposition. We ought to pay attention not only to the patient, but also to his relatives. Since by thorough questioning we are only able to recognize a small part of the latent cases, the physician ought to become acquainted with the simple methods by which an earlier diagnosis of the diabetic disposition is possible. The most simple method is the determination of the fasting blood sugar. More improved is the diagnosis of a latent diabetes by the dextrose tolerance test. Of course, other diseases exerting an influence upon the blood sugar curve must be excluded beforehand. The chance of a prophylactical-therapeutical success in diabetes candidates is great. Subjective and clinical manifestations of the disease can be prevented. Therefore the different exogene factors, environmental influences which cause the advance and slackening of the development of diabetes and obesity must be recognized. The old dietetic treatment, in former times the only treatment at our disposal, retains its full value in this respect. Early restriction in the administration of nourishment is necessary. We must be cautious against overfeeding with fat and exaggerated administration of carbohydrates, especially cakes and sweets. Every peasant knows that we are able to fatten animals by abundant amounts of carbohydrates. Vegetables and fruits should be preferred in the food. Obese persons with latent diabetes have to be calorically underfed, but they ought to get a sufficient amount of carbohydrates. Underfeeding too greatly intensified regarding the calorical values and a suggested withdrawal of protein must be avoided in regard to diabetes candidates. Joslin says: "Relatives of diabetes must be instructed never to allow their weight to go above the normal standard, and in fact after the middle of the fourth decade to keep the weight 5 to 10 per cent below such standards." Of importance is the right choice of profession. Sedentary occupations are to be avoided. Where there is

significant alterations from the normal. There is no royal road to an easy differential diagnosis of abdominal distress.

12. Case reports are given to illustrate some types of cardiovascular disease that give rise to pronounced gastro-intestinal symptoms.

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Fundamental Facts of the Prophylaxis in Diabetes Mellitus

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JERUSALEM, PALESTINE

THE doctrine of diabetes is still full of doubts and contradictions and burdened with many a prejudice. We have seen in recent years a continuous wavering in regard to the fundamental pathogenetic and therapeutic views on diabetes, and in the future also we can expect surprises in this respect. The views on the prophylaxis of diabetes depend to a great extent upon the different theoretical views of the investigators.

Diabetes is a recessive disease, which originates from the hereditary disposition and it can be traced to a defective disposition of the insular apparatus of the pancreatic gland. On the other hand some well-known investigators favor the hypothesis that diabetes is often an acquired disease. The characteristic feature of diabetes is the lack of insulin; the most direct and important consequence of this lack of insulin is that the formation of glycogen in the cell—above all in the musculature, less in the liver—is being made difficult. The recessive hereditary disposition has been proved by investigations regarding family-pathology and twin-pathology. The discordant behaviour of enzygotic twins indicates the influence of environmental factors. The complete disharmony of behaviour of enzygotic twins has to be explained by unusual oscillations in manifestation (Störring). Heredity is the basis of diabetes, as Joslin says. He and his co-workers, White and Pincus, believe that it is highly probable that the development of diabetes depends primarily upon the transmission of the single recessive gene and the operation of one or more secondary factors. Pannhorst draws conclusions from the hormonal connections and from the variety of origin and severity; he thinks that among others not a single Mendelian gene, but probably "multiple allele" are decisive for the hereditary disposition of diabetes.

The question of the apparent or absolute increase of diabetes occupies a large space in modern literature. The graduated aging of the population, the reduction in the mortality from acute diseases, the improved early diagnosis of diabetes and better treatment, the consideration of social conditions led to an increased frequency and hence to an apparent relative increase in the number of diabetics. The absolute increase in diabetes is not due to a real increase of the hereditary disposition. The greater absolute frequency of diabetes is explained by an increased effect of exogene factors, which, in their turn, cause the disease. As causes are named the increased consumption of fat, the migration from agriculture into the towns, into professions with insufficient bodily exercise. Joslin thinks that "the increase is absolute as well as relative and that through a multitude of causes which lead to it, obesity brought about in a multitude of ways by our modern civilization is the chief inciting factor." "The hereditary tendency to diabetes is potential, a provocative force is required, before it becomes manifest."

He judges the influence of occupation also according to the opportunity of producing overweight. According to Lawrence "among the more immediate causes the most noticeable are over-eating and obesity." "The underweight is an insurance against diabetes."

It is well-known that some obese persons get sugar with the exactness of an experiment as soon as their weight exceeds a certain limit (Grafe). Juvenile obesity especially frequently develops into diabetes, and obese families are frequently diabetic families. It has been assumed that an exhaustment of the increte production could perhaps occur by exaggerated use of the increte production over many years by over-feeding (Thannhauser). Van Noorden and Isaac state, like many others, the frequent simultaneous occurrence of diabetes and obesity, refuse, however, to place obesity due to over-feeding in the forefront of diabetes etiology, so to say, to identify the exciting cause of exogene obesity and diabetes. According to Joslin, heredity seems to be the most important link in the chain of diabetes from generation to generation. But he speaks of obesity as having central importance. "In the adult obesity brings out the predisposition to the disease." "Obesity is preventable." Therefore it is within our power to avoid diabetes. The experiment of the Great War, during which diabetes was reduced by lack of nourishment in Germany, would favour this hypothesis.

Submitted March 3, 1937.

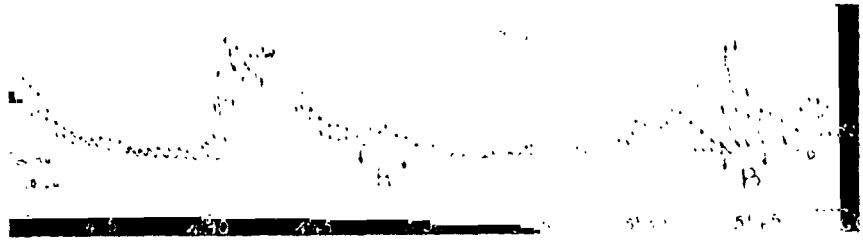


Fig. 1. Dog's colon, showing "B," increased muscular activity stimulated by the taking of food by mouth. (Feeding reflex) "A" shows the absence of the feeding effect when fed through a gastric fistula, showing that this reflex is not a gastrocolic reflex but a true appetite or taste reflex.

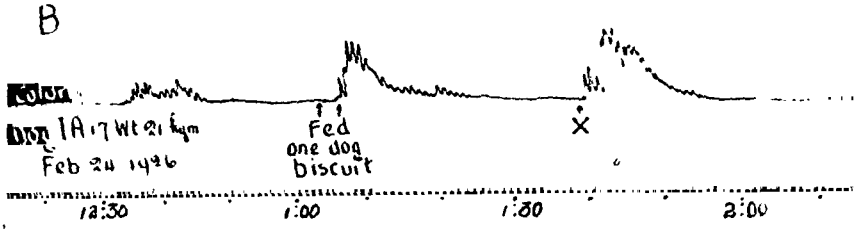


Fig. 2. Colon tracing dog, showing typical feeding reflex and a second psychic reflex at "X," initiated by the entrance of the dog's keeper who regularly fed the dogs.

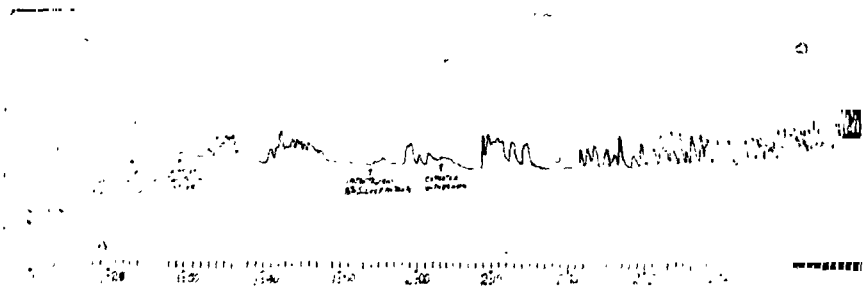


Fig. 3. Tracing of normal human colon showing increase in peristalsis and tone associated with trauma to the right ureter. Twisting of the catheter in the ureter caused painful contractions to occur in the colon on the left side of the abdomen. Injection of 6 c.c. of ½% silver nitrate caused further increase in muscular activity of the colon consisting of tone changes and painful contractions. These continued until they reached such severity as to require an opiate. The painful contractions in the colon occurred with pain in the right kidney tract and independent of the pain in the right kidney tract.

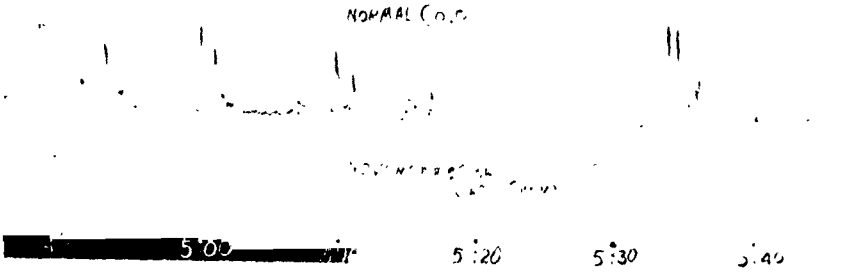


Fig. 4. Normal tracing human colon showing infrequent contractions and almost complete absence of tonal changes. Water pressure one inch.

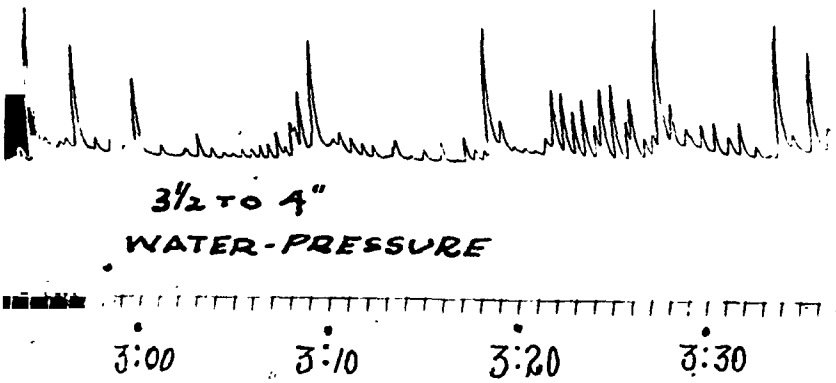


Fig. 5. Normal human colon tracing showing increased muscular activity produced by moderate distention of colon walls.

spasm of the colon. The correction of constipation by the removal of a diseased appendix or gall bladder has doubtless come within the experience of all of us. The association of rectal tenesmus with the strangury of cystitis or a diseased prostate has been a common experience. Distention of the normal sphincter ani regularly causes reflex increase in muscular activity of the colon higher up, particularly in the rectum. The ureters are frequent sources of reflex stimuli to the colon. In one instance during catheterization of the right ureter, the colon was stimulated to violent activity resulting in defecation during the cystoscopy.

The relationship between urologic disease and digestive symptoms has been investigated by the author and associates in urology. Studies were made of the effect of ureteral trauma upon the muscular activity of the colon. A volunteer woman with a permanent colostomy was used. A recording balloon was inserted into the proximal loop of colon through the colostomy; a kymographic tracing of the colon was made in the usual manner. After the colon had accommodated itself to the presence of the balloon, the patient was cystoscoped and a ureteral catheter was quickly passed to the pelvis of the right kidney. The catheter was then twisted to produce irritation in the ureter. Silver nitrate ½ of 1% was injected in the amount of 6 c.c. and the catheter was withdrawn.

During the insertion of the cystoscope and ureteral catheter, there was an apparent inhibition of colon peristalsis. Twisting of the catheter produced an aching pain in the region of the right kidney followed shortly by painful contractions of the colon on the left side at the site of the balloon. Injection of silver nitrate was followed by still further contractions in the previously resting colon. These contractions increased in amplitude and frequency. Each contraction of the colon was accompanied by left sided pain, with or without pain in the right kidney tracts (Fig. 3).

These painful contractions in the colon probably represent the mechanism of production of symptoms apparently arising in the colon associated with obstructive lesions in the ureters.

Apparently the ureter, rather than the kidney pelvis, is the chief source of this reflex irritation, as trauma of the kidney pelvis alone produced relatively slight reaction in the colon, whereas trauma of the ureter, produced by twisting the ureteral catheter and the injection of silver nitrate, caused marked changes in the muscular activity. These changes consisted of increased frequency and amplitude of peristaltic contractions and a very definite elevation in muscular tone.

INTRINSIC FACTORS INFLUENCING THE MUSCULAR ACTIVITY OF THE COLON

While studying the effect of feeding on the muscular activity of the colon, marked variations were found to occur. These variations were influenced largely by the character and amount of residue occupying the lumen of the colon. When the colon was completely empty and a small recording balloon was inserted within its lumen, the muscular tone of the colon was uniformly low and periods of peristaltic activity were few and usually of low amplitude and short duration due to the absence of distention or irritation.

When the colon was full of fecal material and a balloon was introduced, or when a very large balloon alone was used, the muscular activity was excessive with marked and very irregular tone changes with superimposed, usually exaggerated, peristaltic waves with very short periods of relaxation.

A recent study of the effect of distention upon the muscular activity of the colon has been made by the author in humans who had permanent colostomies. In this series of experiments, five negro women so operated upon were observed.

Condom balloons were inserted into the colon, both proximal and distal to the colostomy openings. The balloons were distended with water with varying levels of hydrostatic pressure controlled by a separatory funnel. The changes in muscular activity were recorded on the kymograph with the recording device which the author has perfected.

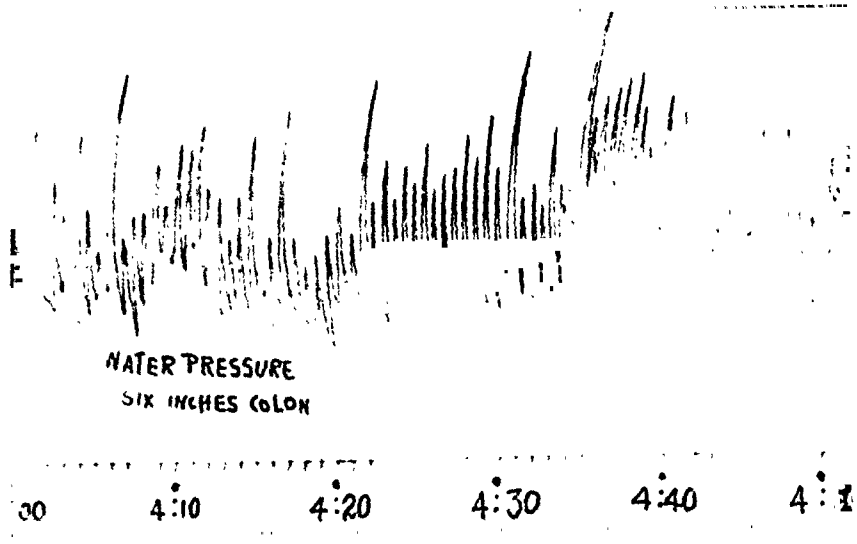


Fig. 6. Tracing normal colon, showing marked increase in muscular activity of the colon consisting of rapidly recurring deep peristaltic waves with definite tone changes.

With a water pressure of one inch or less, the colon was quiescent most of the time with occasional contractions without much tone change. These contractions occurred irregularly and were usually of short duration (Fig. 4).

Increase of the water pressure in the thin walled elastic condom balloon invariably increased the frequency of contractions and the tone changes. The increase in the muscular activity of the colon was proportional to the increase in water pressure and distention of the bowel wall.

The changes in the muscular activity of the colon varied with the degree of distention from a moderate increase in frequency and amplitude of contractions to a continuous activity with constant, rapid and extensive contractions with well marked tonal changes as shown in Figs. 5 and 6.

The degree of increase in muscular activity varied in different colons and also in the same colon at different times but was always similar in character. These tracings were made in quiet surroundings, the subject lying comfortably and relaxed, usually sleeping while the prolonged tracings were being made.

EFFECT OF PROLONGED DISTENTION UPON THE MUSCULAR ACTIVITY OF THE COLON

With prolonged distention, the irritability of the colon gradually lessened, the tonus slowly lowered, the intervals of contractions were of shorter duration and less extensive until usually within one to two hours the tracing resembled a resting colon with normal pressure (Fig. 7).

Lowering of the pressure within the colon lumen for several minutes followed by an increase in pressure usually resulted in several small contractions followed by prolonged rest.

This loss of irritability of the colon musculature after prolonged distention is probably similar to that observed in the rectum, when the call to defecation having been repeatedly ignored the defecation reflex becomes depressed or sometimes almost completly obliterated. It is possible that this loss of irritability

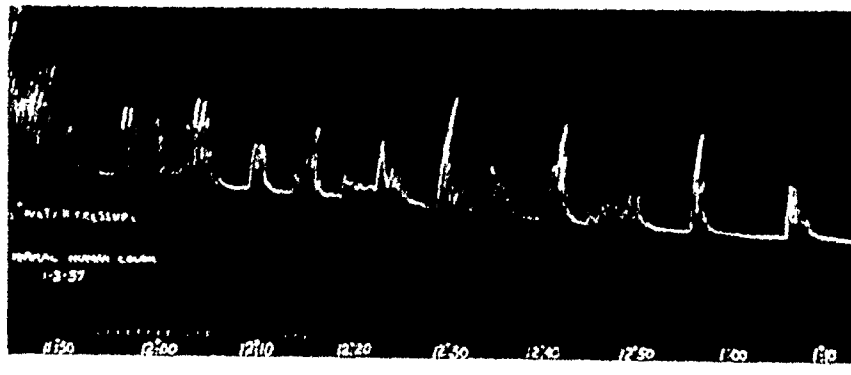


Fig. 7. Tracing of the normal human colon showing the effect of prolonged distention upon the muscular activity, consisting of wider intervals between peristaltic contractions and a gradual slow loss of tone, wider resting intervals between periods of contraction.

may be responsible for stasis in the proximal colon and cecum. Certainly the colon is not in spasm after prolonged distention and it may be that our conception of colon stasis as almost always being "spastic" in origin is a miscomprehension. It is not likely that the smooth muscle of the colon has become fatigued in this short period, for distention for a period of less than two hours usually sufficed to produce inhibition of peristalsis and tonus. It is more likely that this apparent inhibition is due to loss of irritability of the neuromuscular apparatus. Studies of the reaction of the denervated gut have not been made by the author.

The increased activity of the colon musculature with distention is certainly intrinsic and represents in part, at least, the characteristic response of isolated smooth muscle to mild stretching. Bayliss and Starling (7) in 1901 stated that "peristalsis in the denervated gut was started by the stimulation of local nerve plexuses by the presence of a stimulating agent within its lumen."

Irritating substances introduced into the colon likewise cause marked changes in activity. Plant and Miller (8) found that "introduction of cinnamon water (U.S.P.) caused a distinct rise in the tone accompanied by an increase in amplitude of the large contraction waves." The introduction of even isotonic solutions of magnesium sulphate into the dog's colon produced a marked increase in muscular activity, possibly by distention.

It is improbable that normal fecal residues ever distend or irritate the normal colon as was done in these experiments but it is possible that the stuffing of patients with irritable colons, with high residue and roughage diets does produce an aggravation of the already existing irritability both by distention and local irritation similar to that produced experimentally.

Prolonged retention of large fecal residues probably eventually raises the threshold of irritability of the colon and may produce stasis not only at the rectum but in any part of the colon where such prolonged accumulations occur by loss of excitability of the neuromuscular apparatus.

These observations indicate that the amount and character of residues within the lumen of the colon are potent factors in determining the character of its muscular activity and must be recognized and appreciated as fundamental factors in any course of management intended to correct colon disorders.

SUMMARY

It has been shown that the muscular activity of the normal colon is influenced by many factors, both extrinsic and intrinsic.

It has been shown that feeding by mouth produces a reflex activity in the colon and that feedings through a gastric fistula produce no reflex and that this is an appetite or taste reflex and not a gastrocolic reflex.

The effect of psychic stimuli upon the colon musculature has been discussed.

It has been shown that stimuli arising in adjacent viscera have a profound influence upon the muscular activity of the normal colon.

The effect of distention upon the colon musculature has been shown; also the effect of prolonged distention has been shown and discussed.

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Human Autonomic Pharmacology

8. The Effect of Iontophoresis on the Gastric Juices with especial reference to Acetyl-Beta-Methyl Choline Chloride (Mecholyl)*

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THE use of the galvanic current for the introduction of drugs through the skin began with the investigations of Frankenhäuser (1) in 1898. His studies were followed a few years later by those of LeDuc (2). This method of therapy became known as iontophoresis. Since this early work, numerous publications on the theoretical and clinical aspects of iontophoresis have been written. Especially has the method been used in the field of ophthalmology, where it was introduced in 1908 by Wirtz (3). Many other workers, including Schnyder (4), Bos (5), and Erlanger (6), have utilized iontophoresis with various drugs in diseases of the eye.

One of the most recent drugs introduced into the body by the technique of iontophoresis is acetyl-beta-methylcholine chloride or mecholyl, particularly in the treatment of arthritis, peripheral vascular disease, myositis and skin ulcers, Kovacs (7), Abel (8), Saylor, Kovacs and Duryee (9). Kotkis and Melchionna (10) observed the effects of mecholyl iontophoresis on dogs. They concluded that the positively charged part of the mecholyl molecule is liberated at the positive pole of the galvanic current into the capillaries of the skin where it is probably taken up by the blood. Their control experiments, in which physiological salt solu-

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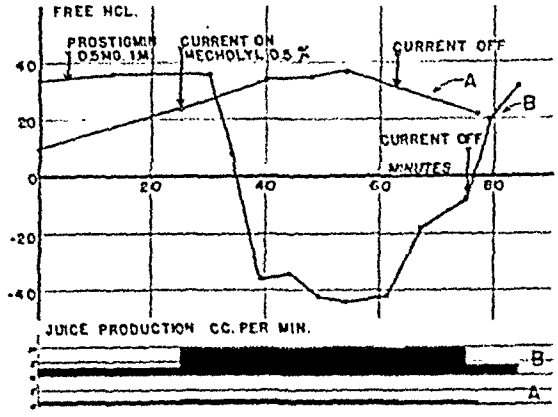


Chart 1. The effect of iontophoresis on the gastric juice with (a) mecholyl alone, and (b) with prostigmin and mecholyl. In this subject mecholyl alone was not effective in diminishing the acidity of the gastric juice, but when it was combined with prostigmin the juice became rapidly alkaline and increased in amount. These changes continued for approximately forty minutes, when the current was turned off.

tion was used in place of the mecholyl, gave negative results.

Kovacs (7) observed that a 1% mecholyl solution applied over arthritic joints causes the following local and general changes: local sweating for a period of eight to ten hours, increased temperature of the skin, an increase in capillary flow without enlargement of the capillaries, slight redness of the skin, a questionable slight increase in the leukocytic count, a feeling of warmth, a reduction of the swelling, increased mobility and relief from pain. Flushing, generalized sweating, increase in pulse rate, salivation, slight lowering of blood pressure, and evidence of intestinal peristalsis occurred. That the drug penetrates the skin through the positive galvanic pole has been definitely demonstrated by Alexander and Kotkis (11), who found that a substance identical in its physiological action with mecholyl was present in the perfusate in the hind limbs of animals following iontophoresis.

The introduction of mecholyl into the body by iontophoresis may be compared to a widespread intradermal injection of the drug (12). By either method two effects are obtained: (1) a local sweat reaction, and (2) if the dose is sufficient, general effects of the drug are obtained. Thus, we have demonstrated that if an electrode the size of a quarter is used as the positive pole, a local sweat reaction at the zone stimulated and practically identical with that resulting from a local intradermal injection with mecholyl is obtained. If several intradermal injections of very dilute solutions are made on a subject, not only does a local sweat reaction develop, but general sweating and all the other effects produced by a moderate to a large subcutaneous injection of the drug appear.

In a previous communication Myerson, Rinkel and Dameshek (13) definitely demonstrated that mecholyl alters the character of the human gastric secretion so that the quantity increases, the acidity diminishes, pepsinogen disappears, and mucus appears in large quantities. These changes in gastric function were observed to be as rapid in their occurrence as were the other manifestations caused by the injections of mecholyl in doses between 20 and 30 mg. and wore off in about the same length of time. Furthermore, it was shown that the changes in gastric secretion could be completely prevented or abolished by atropin and enhanced by the administration of physostigmin or prostigmin. For example, 1/50 to 1/100 gr. of atropin given simultaneously with or prior to the injection of mecholyl regularly checked the production of an alkaline mucus juice as promptly as it did the other effects of the drug. Again, when given at the height of the mecholyl reaction, atropin caused a rapid return of the juice to its original character. On the other hand, doses of mecholyl too small to be very effective in changing the reaction of the gastric juice, when combined with prostigmin or physostigmin, created as marked changes in the gastric secretion as did moderate to large doses of mecholyl alone. The synergism of prostigmin and mecholyl is as regular as the antagonism of mecholyl and atropin not only on the gastric function but also on the other autonomic functions of the body which we have studied. It should be emphasized here that although it is usually safe to give mecholyl in dosage of 25 mg., it is definitely hazardous to give more than 10 mg. of the drug when combined with prostigmin.

Because mecholyl when given by the parenteral route is explosive and quite transient in its effects, the method of iontophoresis was utilized in the present study in an attempt to produce slower and more prolonged changes in the gastric juice. In addition, the present study includes the use of benzedrine, histamin, and prostigmin introduced into the body by iontophoresis.

MATERIAL AND TECHNIQUE

The same group of subjects who were given mecholyl by subcutaneous route in the study by Myerson, Rinkel and Dameshek (13) were utilized. The experiments were carried out under similar basal conditions. Before the application of the electrodes, a stomach tube was passed and maximum amounts of gastric juice removed at short intervals. The juice was examined for free hydrochloric acid, combined and total acids and, in a few instances for its pH con-

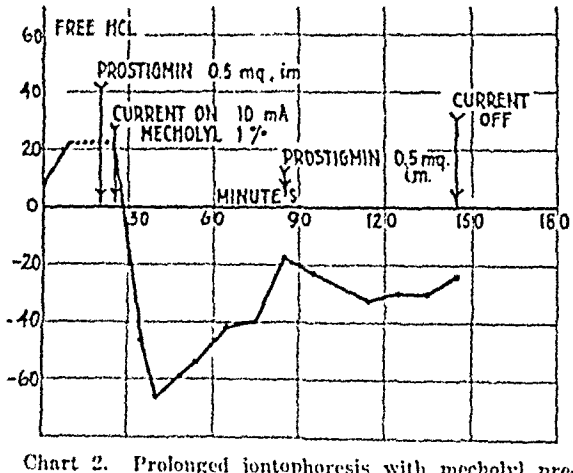


Chart 2. Prolonged iontophoresis with mecholyl preceded and followed by prostigmin. The gastric juice remained alkaline for approximately two hours, when the current was discontinued.

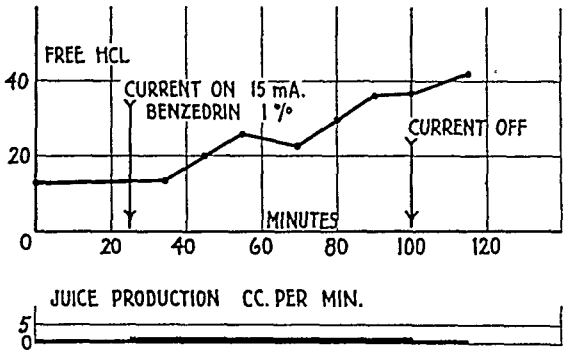


Chart 3. The effect of iontophoresis with benzedrine: An increase in gastric acidity associated with slight increase in the production of juice occurred.

centration. Large rectangular electrodes, measuring 8.5 inches by 6.5 inches, the positive one placed over the abdomen and the negative one over the lower back, were used. The electrodes were wrapped in gauze and finally covered by rubber sheeting which encircled the abdomen. The positive electrode was kept saturated with either mecholyl, usually a 1% solution; benzedrine, a 1% solution; histamin, a 1:10,000 solution; and prostigmin, a 1:2000 solution. The negative electrode was saturated with normal salt solution. After all the juice obtainable was removed, the current was applied, usually in the strength of 15 milliamperes and at short intervals maximum amounts of gastric juice were recovered. In most instances in which mecholyl was used, the subjects previously received prostigmin (0.5 mg.) or physostigmin (gr. 1/100) by subcutaneous route. When prolonged administration of mecholyl by iontophoresis was carried out, the gauze covering the positive electrode was removed at one hour intervals and saturated with fresh mecholyl solution. The blood pressure, pulse, and the visible effects of the drugs were noted throughout the experiment.

RESULTS

1. Control observations. In order to determine whether the changes noted in the gastric juice were due to the penetration of the drug itself and not to other factors involved in the experiment, the following observations were made:

(a) The effect on the stomach juices of galvanization with either water or salt: In several instances it was observed that no specific changes occurred in the acid level or quantity of the gastric juice.

(b) The factor of heat created by the galvanic current applied to the skin: In several subjects the gastric juice was examined following the application of a hot water pad over the abdomen. Under such conditions no definite changes were noted in the character of the gastric juice.

2. Iontophoresis with mecholyl.

(a) The administration of mecholyl by iontophoresis was carried out in the following manner on three subjects:

In the case of the first subject, who was given 1% solution of mecholyl by this method, a fall in the free HCl of the stomach juice from 12 to an acid deficit of 14 resulted. Associated with this change there was a slight generalized perspiration. Later, the same subject was given 1.3 mg. of atropin subcutaneously prior to the mecholyl iontophoresis. No significant change in the gastric acidity now resulted.

In another subject, iontophoresis with a 5% solution of mecholyl and with a current of 30 milliamperes resulted in a change of the gastric pH from 1.91 to 8.33, associated with moderate generalized perspiration.

In the third subject, no change in the gastric secretion occurred, when a 0.5% mecholyl solution was used, but later a definite drop in the acidity to the alkaline side (from 34 to -42) occurred when the mecholyl iontophoresis was preceded by the administration of prostigmin (0.5 mg.) (Chart 1). Accompanying this change there was moderate generalized sweating.

(b) In ten other subjects the mecholyl iontophoresis (1%) was preceded by a subcutaneous injection of prostigmin (0.5 mg.). In every case there resulted a rapid disappearance of free HCl from the stomach and an increase in the mucus content, these changes lasting from forty minutes to longer than one hour (Table I).

The quantity of mucus produced by the stomach was comparable to that observed when the drug was given by subcutaneous route. Most of the ten subjects exhibited moderate to marked perspiration. Samples of gastric juice taken at various intervals following the administration of the prostigmin showed no change towards the alkaline side. The sudden changes in alkalinity and the increase in mucus occurred soon after the administration of mecholyl, usually within ten minutes. The pulse rate was observed to increase in all but two of the cases in which it was followed, the increase varying from 12 to 42 beats per minute. One case showed a secondary slowing of pulse. In four cases a drop of blood pressure ranging from 16 to 30 mm. occurred.

(c) In two subjects the period of iontophoresis was extended for approximately two hours (Chart 2). It was found that the alkalinity of the gastric juice could readily be maintained and controlled by: (1) repetition of the dose of the prostigmin an hour after the first injection; (2) renewal of the mecholyl solution; and (3) adjustment of the strength of the

TABLE I

Iontophoresis

Case	Initial Acidity	Period of Pre-Alkalinity	Period of Alkalinity	Maximum Acid Deficit
J. Ca.	64	7 min.	39 min.	—40
J. Pr.	36	12 "	97 "	—24
H. Br.	24	10 "	45 "	—14
A. Fe.	15	5 "	70 "	—30
P. Co.	8	16 "	57 "	—24
C. Pe.	22	18 "	74 "	—20
J. McG.	4	10 "	85 "	—24
J. Ca.	44	5 "	74 "	—40
J. Ma.	8	5 "	57 "	—40
A. McN.	30	10 "	56 "	—38

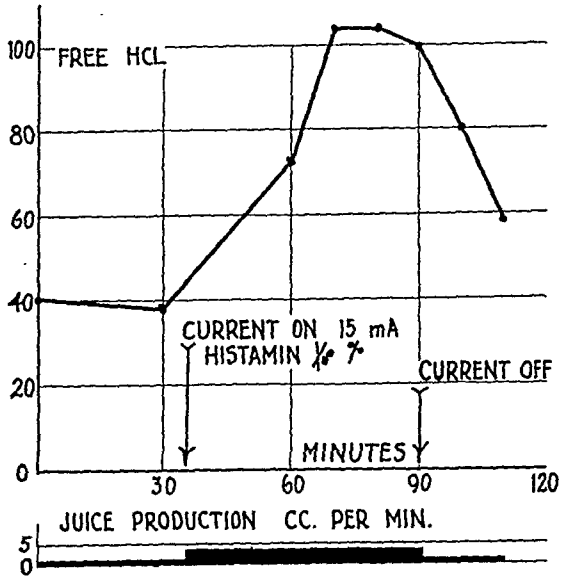


Chart 4. Iontophoresis with histamin: Note the marked increase in gastric acidity associated with the increased production of gastric juice.

galvanic current. Since the juice becomes alkaline with the appearance of the general effects of the mecholyl, the current was adjusted to the lowest milliamperage necessary to produce slight sweating of the face. Thus, a milliamperage between 5 and 10 was found to be sufficient to keep the gastric juice at an alkaline level. By this technique, the discomfort to the patient was minimal over a period of two hours or longer.

3. Iontophoresis with benzedrine. Benzedrine was administered by iontophoresis to four subjects. The experiments were followed for approximately two hours. Only two subjects showed a significant increase in gastric free HCl. There was, however, a rise in blood pressure in every case ranging from 9 to 34 mm. of mercury, which indicated that the benzedrine had been absorbed (Chart 3).

4. Iontophoresis with histamin. For comparison with benzedrine, two subjects were given histamin (1:10,000) by iontophoresis. In the first case, the free HCl rose from 7.5 to 114. No change in pulse or blood pressure was noted. In the other subject, there was a change in the free HCl from 38 to 104, associated with a fall in blood pressure of 20 mm. of mercury, but with no change in pulse rate (Chart 4).

5. Iontophoresis with prostigmin. Prostigmin (1:2000) by iontophoresis was administered for approximately one hour to two subjects. No specific effect in the gastric juice was noted in either case, the HCl showing normal variations throughout (Chart 5).

COMMENT

The foregoing results indicate definitely that the changes produced in the gastric juice by mecholyl iontophoresis, particularly when preceded by the administration of prostigmin are comparable with the changes produced by a subcutaneous injection of the drug, namely, the production of an alkaline mucous juice usually within ten minutes following the beginning of iontophoresis which is associated with the general effects of sweating, increase in pulse rate, and fall in blood pressure. The administration of the drug by iontophoresis, however, is capable of more prolonged and not so explosive effects as it is by the subcutaneous route, since the drug is more slowly absorbed and better controlled by the former method. It is, therefore, not so apt to cause sudden drops in blood pressure as by subcutaneous administration. For these reasons the method of iontophoresis is the one of choice for the administration of the drug in its possible therapeutic use for gastric ulcer in which an alkaline gastric juice is desirable. Prolongation of the alkaline mucous gastric juice for periods of two or more hours can be effected by repeated subcutaneous doses of prostigmin followed by replenishment of mecholyl solution on the positive electrode and adjustment of the strength of the current. By these means a slight generalized reaction can be maintained with the minimum discomfort to the patient. Since the point at which the gastric juice becomes alkaline corresponds with the onset of the general effects of the drug, perspiration may be taken as an index of the reaction of the juice. Thus, if mecholyl iontophoresis is used as a method of therapy in gastric ulcer, intubation would be rendered unnecessary. The administration of prostigmin prior to the mecholyl iontophoresis is highly recommended since with mecholyl alone production of a mucous juice may not be sufficiently marked or regularly obtained in some instahces (14). It is clear that the effects described above are definitely due to the penetration of mecholyl into the body, the other factors of the method playing little or no important role.

The results obtained by iontophoresis with benzedrine are not so striking as those obtained by mecholyl. The observations made on the four subjects studied indicate that there is a slight increase in the acid level of the gastric juice, but this is not so clearly evident as when the drug is administered by subcutaneous injection (15). That the benzedrine enters the body by iontophoresis is, however, indicated by the fact that there is a definite rise in blood pressure

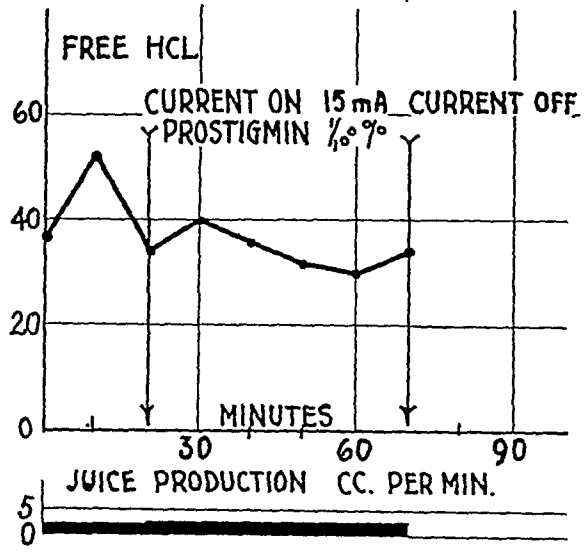


Chart 5. Iontophoresis with prostigmin: There is an insignificant effect on the level of acidity and production of the gastric juice.

associated with the slight increase in gastric acidity. It is obvious that the drug, when given by iontophoresis, does not penetrate the body in sufficient quantity to create as great changes as it does following a subcutaneous injection (13).

The alterations in the gastric juice following histamin iontophoresis are as striking as those obtained by mecholyl iontophoresis. The histamin molecule obviously very effectively penetrates the body, creating as marked an increase in the gastric acidity as is obtained following the subcutaneous administration of the drug.

Although prostigmin given by subcutaneous route is capable of producing an alkaline gastric juice, it does so very slowly and in much longer time than does mecholyl itself. These observations have been made by Myerson, Rinkel and Dameshek (13) in the previously mentioned study. By iontophoresis, prostigmin does not appear to penetrate the body, at least in sufficient quantity to cause any definite change in the gastric juice.

CONCLUSIONS

1. The administration of mecholyl by iontophoresis produces an alkaline mucous gastric juice as effectively as it does when given by subcutaneous injection. Furthermore, the method of iontophoresis with mecholyl for the production of an alkaline juice has distinct advantages over its administration by subcutaneous route, namely, the effects of the drug are not so explosive; the drop in blood pressure is not so sudden or marked; and the period of time of the alkalinity is markedly increased. For these reasons the former method would appear to be the method of choice for its possible therapeutic application in gastric ulcer. The administration of prostigmin before iontophoresis of mecholyl is strongly recommended, since the effects of mecholyl are regularly enhanced. By the use of these two drugs the alkalinity of the gastric juice can be maintained for two hours or longer.

2. Iontophoresis of benzedrine causes a slight increase in the acidity of the gastric juice associated with a rise in blood pressure. These changes are not so marked as when the drug is administered by parenteral route.

3. The administration of histamin by iontophoresis results in a much greater increase in gastric acidity than does benzedrine.

4. The administration of prostigmin by iontophoresis causes no significant changes in the acid level of the gastric juice.

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Electro-Coagulation of Rectal Cancer*

By

R. PITANGA SANTOS, M.D.†

IN the treatment of rectal cancer we can from the outset exclude radium and X-rays. Radium is difficult to use in the requisite amount. Even when well placed with the help of the proctoscope, it is not easily kept *in loco* for the necessary length of time, on account of contractions of the rectum. Furthermore, the mucous membrane of this organ is very sensitive to radium. This sensitiveness can be noted even when radium is applied to adjacent regions. I have known cases in which the use of radium on the cervix of the uterus has produced intense rectitis with early stricture, and sometimes deep necrosis, with eschar formation on the rectal wall. In the last three years I have found three cases of this kind. The difficulty of keeping radium tubes in place (on the affected area) makes its use in the rectum dangerous.

X-rays cannot reach the tumor in sufficient dosage, on account of the deep location of the rectum and of the bony pelvis that surrounds it. The disadvantage of direct application through a tube inserted into the rectum, such as the Schaefer-Witte apparatus, is that the patient cannot endure it because the application

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takes a long time. It would be possible only with a million-volt apparatus, permitting a short treatment of 3 or 4 minutes. However, such an apparatus is very expensive and the treatment would be economically of great cost.

There remain surgery and electrocoagulation. Other treatments have been employed; we are now attempting pasteurization of the tumor by means of short waves. The results are still too uncertain and recent to be reported.

There is also the compressed-oxygen treatment, which Prof. Osorio de Almeida has been using with satisfactory results (according to the author). This treatment, unfortunately, necessitates high-voltage X-rays. It is slow and costly, and in many cases cannot be employed. Moreover, results for rectal cancer have not proved satisfactory, at least until a short time ago. Recently the author has used radium together with oxygen, and has seemingly had better success. In any case, it is not a practical method because it is drawn-out and expensive.

As for surgery in rectal cancer—the earlier the operation the better the results. Unfortunately, this is not always possible. Early diagnosis is generally a matter of chance, because rectal cancer develops quietly during the first few months. Its only usual symptom does not alarm the patient: stubborn constipation. It causes neither pain nor pressure nor bleeding. If, by chance, a doctor is consulted, he likewise suspects nothing, in view of the absence of other symptoms. Therefore, the surgeon has an opportunity to operate only on very advanced cases. Nevertheless, surgery in rectal cancer is, in the majority of cases, successful. Therefore I am not trying to combat surgery, for I have resorted to it myself on several occasions. Still, it has fewer advantages than has coagulation. It is a more serious operation, more hemorrhagic and more subject to recurrence of the malady.

With electrocoagulation the operation can be performed without loss of blood and without shock to the patient. Even under the poorest conditions of operability, the patient emerges looking none the worse. Furthermore, it is an economical operation. When conditions are identical, given an incipient cancer in the rectal ampulla, surgery removes the whole rectum, from the anal to the sirmoid, whereas electrocoagulation destroys only the tumor and preserves the rest of the rectal ampulla.

Often this operation can be performed at one time, and only in very advanced cases is it necessary to fashion an iliac anus. My experience in coagulation leads me to prefer it to surgery. I have made 35 coagulations on very advanced tumors without a single death from operation. Of these 35 coagulated cases, 8 died of metastasis; 27 are living:

1 has been cured 7 years.
4 have been cured 6 years and 8 months.
3 have been cured 6 years and 2 months.
1 has been cured 6 years and 3 months.
1 has been cured 4 years and 9 months.
3 have been cured 3 years and 6 months.
2 have been cured 2 years and 9 months.
2 have been cured 2 years and 6 months.
5 have been cured about 5 years.
5 were coagulated this year

The technique and instruments of diathermo-coagulation are well known. I use an apparatus of 6 amp. because our service does not permit the use of a stronger one. There are apparatuses of 20 amp., like that of Kayser in Berlin. With a 6 amp., coagulation is slower and more laborious, but good results can be obtained. The tumor is coagulated progressively from the surface downward. As the tissues become coagulated, they must be curetted, because if a thick layer of coagulated tissue is allowed to remain, the deeper tissues will not be destroyed. The electrocoagulator must be constantly cleaned, because coagulated tissue adhers to it. The technique is slightly blind. One works with a diathermo-coagulator as with a curet in osteomyelitis. Cancerous tissue is coagulated more easily than healthy tissue; in that way one knows when one has reached normal tissue. The only safe rule is to proceed cautiously, attentively and slowly. The only guide is the hardness of the tumor, which contrasts with the adjoining tissues. A digital examination must therefore be made from time to time. In the lower half of the ampulla, nothing need be feared. In the upper half, however, one runs the risk of perforating the bladder or the peritoneum. Yet this will occur only when the tumor extends to those regions. That has never happened in the coagulations I have performed.

When the tumor has been destroyed, the last layer of coagulated tissue should not be scraped. So that when the scar sloughs off, the surrounding tissues are protected by a defense layer and the peritoneal cavity will not be perforated. At least, that has always been so in my cases.

There remains the problem of perirectal adenopathy. As a rule I disregard it. In the great majority of cases, such adenopathy is only inflammatory. This fact has been proved by numerous authors and my experience agrees fully with theirs. Furthermore, cancer develops slowly in depth. It develops circumferentially, spreading over the mucous membrane of the rectum.

Lenthal Cheatle, surgeon in King's College Hospital, London, published in the February, 1914, issue of the *British Medical Journal*, an article with numerous microphotographs, showing longitudinal and transverse cuts of a rectal cancer, in which it is evident that cancerous cells are nonexistant adjoining the tumor. Penetration through lymphatic channels is also very slow, because we see large rectal tumors operated upon without emptying these ganglia and with a survival of 5 to 6 years and no local metastasis. Furthermore, any pericancerous adenopathy revealed by digital probe may likewise be coagulated.

This is the rule I follow: in incipient cases in which the tumor occupies a small part of the rectal circumference, I coagulate transanally after dilating the sphincter. In more advanced cases, I section the anal canal, in the posterior angle, as far as the coccyx, and I coagulate in the open, as it were. If the tumor occupies only half the circumference, I coagulate only that half, preserving the rest of the rectal ampulla. Healing takes place normally in 30 to 40 days, obtaining also a perfect healing of the anal wound, with the sphincter preserved. If the cancer occupies all the rectal circumference, coagulation must destroy the whole organ. Then a preliminary iliac anus is made which will facilitate the healing of the wound. In these cases, a fibrous tube remains in place of the

rectum. Sometimes this tube is sufficiently elastic to permit closing of the iliac anus. I have three such cases and for six years these patients have been doing well. When that does not occur, the patient keeps the iliac anus permanently.

Surgery could in such cases accomplish a lowering of the sigmoid and thus afford greater convenience to the patient. It is necessary to consider, however, that in these advanced cases the general health of the patient is precarious and such an operation is much more serious than coagulation. For advanced cases, diathermocoagulation, therefore, has the advantage of less risk to operative mortality.

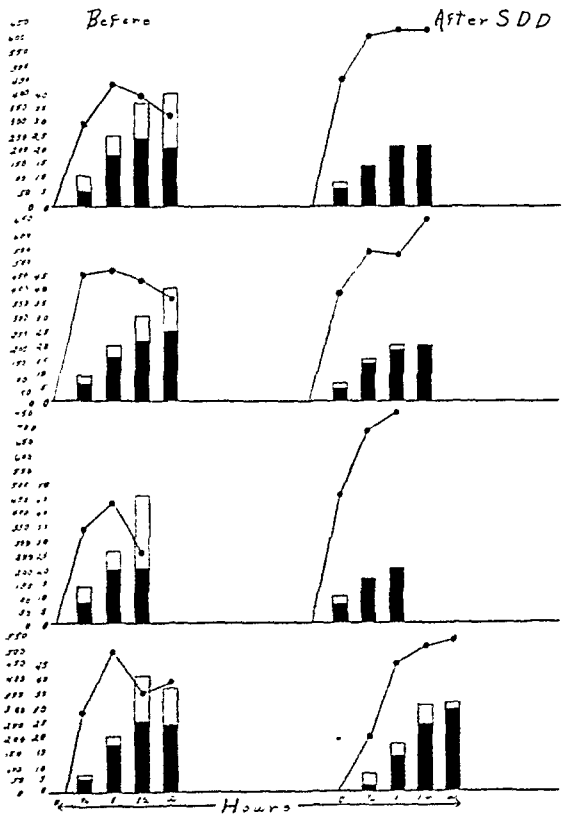
In incipient cases it has the advantage of economy. One can destroy the tumor and keep the rest of the rectal ampulla, performing the operation without perforating ducts or lymphatics, because the tissues are progressively coagulated and curetted. And coagulation is best employed in beginning cases, because in these it is possible to destroy the tumor and preserve the rectum with a relatively small operation.

From this point of view coagulation has all the advantages of the nonsurgical methods (effecting the cure with no risk to the patient), and has the advantage of being easier, more rapid, and more economical.

Editorials

THE DESIRABILITY OF MEASURING THE ACIDITY OF THE GASTRIC SECRETIONS RATHER THAN THAT OF THE GASTRIC CONTENTS

FOLLOWING the administration of a test meal the samples removed from the stomach contain the secretions which entered the stomach mixed with and diluted by a variable and unknown quantity of the fluid given with this test meal; this mixture constitutes the *gastric contents*. It is often, and in fact, usually assumed that the acidity of the *gastric contents* bears a direct and constant relationship to the acidity of the *gastric secretions*. Under many conditions this is not true and the failure to recognize the difference which often exists has led to a great deal of confusion in studies on gastric acidity.



When secretogogues are placed in the stomach, secretion of acid begins rather promptly and may then continue for some time at a fairly high and constant rate, independent of the amount of the meal remaining in the stomach. Thus, in dogs with whole-stomach pouches, secretion may continue for considerable periods of time after the meal has been removed. Variations in the rate of emptying of the stomach may, therefore, cause marked changes in the acidity of the *gastric contents*, due to changes in the proportion between the amounts of test meal and secretions present. Such changes, naturally, need not be related to the changes which are taking place in the acidity of the *secretions* entering the stomach.

The following examples illustrate this point: I. Suppose that two patients are given the same type of test meal which contains 400 c.c. of fluid. Suppose that during the same test period identical amounts of secretion of exactly the same degree of acidity entered the stomach. If the rate of emptying was the same in both patients, then the acidity of the *gastric contents* would be the same in both. Suppose, however, that the rapidity with which the test meal leaves the stomach differs in the two patients, so that the *gastric content* removed from patient (A) consists of the secretions which entered the stomach plus 100 c.c. of the fluid given with the test meal, while in patient (B) only 50 c.c. of fluid given with the test meal is mixed with the secretions. Titration of the *gastric contents* would lead to the erroneous conclusion that patient (A) either secreted only one-half as much acid or that the acidity of his secretion was only one-half as great as patient (B) while in reality the amount and acidity of the secretions were identical and the only difference was that in patient (A) the secretions were diluted by twice the amount of fluid from the test meal. II. Following various surgical procedures the rate of emptying of the stomach is often markedly altered, and due to this fact titration of the *gastric contents* often fails to reveal the true changes produced in the acidity of the secretions entering the stomach. For example, if following a certain surgical procedure the acidity of the *secretions* were to be re-

duced to one-half its original value while at the same time the rate of emptying of the stomach was increased so that only one-half as much fluid from the test meal remained in the stomach to dilute the secretions, then the resultant acidity of the *gastric contents* would be the same as before the operation.

A similar type of reasoning will show that the acidity of the gastric *secretions* might be markedly increased by some procedure but if a corresponding slowing of the rate of emptying should occur, then the acidity of the *contents* would remain unaltered. These examples are not hypothetical but have actually been encountered in experimental work.

The above examples show that the acidity of the *gastric contents* cannot be used to study changes in the acidity of the *gastric secretions*; the two are distinct entities and should be measured separately. When histamine is given and the secretions removed from the empty stomach by continuous suction, it is the acidity of the secretions that is being studied. However, the results obtained in this way are of doubtful significance first, because histamine is the most powerful stimulus known for the secretion of acid and also probably an abnormal one, and under its influence many regulatory phenomena are prevented from exerting their effect; second, in this type of test the normal filling and emptying reflexes are absent and it is well known that they play an important role in regulating the acidity of the gastric secretions.

A better way of studying the acidity of the gastric secretions is to put some substance which is not destroyed or absorbed from the stomach in the fluid of the test meal and to determine the concentration of this substance in the gastric samples. When this is known, it is possible to say just how much of the fluid in the sample of gastric contents is fluid originally given with the test meal and how much is fluid of the secretions which entered the stomach. By dividing the acidity of the contents by the amount of fluid secretions which they contain, the true acidity of the gastric secretions can be obtained.

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GASTRO-ENTEROLOGY AND THE OBESITY PROBLEM

GASTRO-ENTEROLOGY, including the science of nutrition, is the logical specialty to direct medical thought in the problem of obesity and to provide leadership for its proper control. Excessive weight with its associated diseases presents one of the greatest opportunities in the field of personal preventive medicine. Insurance statistics long ago established and have repeatedly re-established increasing mortality rates corresponding quite accurately to increasing degrees of obesity. Two-thirds of all people over forty years of age with fifteen pounds or more overweight show some degree of hypertension. This is controlled to an unappreciated degree by weight reduction. It is extraordinary that these statistics have been so largely ignored by the medical profession. The relationship of excessive weight to such conditions as diabetes, biliary tract disease, certain forms of hypertension, nervous and degenerative disease is undoubted. The numbers of cases in these groups run into the millions and apparently are increasing.

There are innumerable instances of successful and permanent weight reduction in marked obesity under intelligent medical supervision with extraordinary relief from distressing symptoms. It requires only a proper conviction and a little personal force on the part of the physician. With definite instructions and a balanced diet of milk, eggs, whole grain cereal, lean meat, green vegetables, and fruit, of proper total caloric value, it is thoroughly practical in a majority of individuals who seek medical advice, especially a periodic health examination, to attain and maintain a proper weight level. Impersonal propaganda is less effective and often unwisely applied. It is necessary to individualize, to follow the blood pressure in some cases and to see that the reducing program is carried out at a rate and under conditions that permit of proper readjustment of the digestive and circulatory organs. Then, as a rule, the patient has an improved sense of well being during the whole period of reduction.

There are obviously psychological reasons why the matter of obesity is so generally neglected. Some doctors do not like to give unwelcome advice or do what they think will be unpopular with the patient. It is only the superior physician who will persistently pursue the cause of vague symptoms into the field of pathological physiology after he is assured by elaborate tests that there is no organic disease. In the first place, preventive efforts never have the dramatic appeal of specific curative medicine and hence do not compete well for the busy doctor's time and interest unless the humanitarian spirit of service has been developed along with the scientific viewpoint. Moreover the patient may have had a prolonged period of malnutrition or a disease in which full nutrition is desirable. Even the physician in his desire to make the ulcer patient gain weight may forget that a great excess of weight predisposes to the recurrence of ulcer as well as to other troubles.

Indifference on the part of the profession toward obesity and indefiniteness in the matter of dietetic instructions are, however, reprehensible in other respects. Patients turn to dietetic fads, drastic reducing methods, incomplete diets, large amounts of thyroid extract, and even toxic drugs such as dinitrophenol after passing through the hands of regular physicians. Some irregular practitioners by unscientific methods and quite incomplete diets have even temporarily relieved obese patients. Nutritional deficiencies are very prevalent as has been emphasized by Minot and his associates. These deficiencies may exist with obesity and likewise call for scientific dietetic advice from the physician.

Newburg and others have shown by accurate measurement of the energy output and caloric intake that all obese individuals have invariably become fat simply and solely because they have eaten too much for their type and that they will all lose weight with sufficiently reduced caloric intake. The weight can even be predicted quite accurately under fully controlled experimental conditions. Glandular factors, of course, affect basal metabolic rates but are of minor importance in the practical management of obesity. Appetite is no safe guide to nutritional needs. Carlson has shown that the craving for food is largely a matter of memory of pleasant tastes and pleasurable satisfaction. The appetite can really be re-educated and after a period of adjustment the craving for excessive food may be largely lost. It is the problem of overcoming a bad habit. Newburg reported a case of

a 560 pound man reduced over a period of two years to 194 pounds. This patient maintained his weight at 194 pounds in health and at work and stated that he did not crave more food. In many individuals middle age with its decreasing metabolism calls for an intelligent control of eating habits to avoid excessive weight.

Discussions of obesity often sound pedantic and platitudinous and are very apt to end in levity especially when ludicrous figures are exhibited. Consequently, the fact that obesity plays an important part in health and even life is forgotten. It is anyone's privilege, if he chooses, to have the philosophy of "eat, drink and be merry" regardless of obesity but there is no use in deceiving himself as to the facts. He cannot successfully rationalize his follies on the basis of the facts. It is advisable in practice, not to be too arbitrary about normal weight standards but to give plenty of latitude to different types of individuals. There is plenty of obesity beyond such limits. The therapeutic results of weight reduction fully justify the effort. It is really essential to head up a sane, scientific movement in relation to obesity in a responsible organization or group within the profession in order to disseminate sound information in reference to the importance of weight control, complete nutrition and a properly balanced diet.

It is suggested that the gastro-enterological specialty accept the challenge and assume the leadership in an unsensational but persistent campaign for the popularization of weight control in connection with periodic health examinations or any form of personal preventive or curative medicine in private practice.

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THROMBO-ULCERATIVE COLITIS

CHRONIC ulcerative colitis (colitis gravis) is now widely believed to be an infectious disease of the large intestine. A clearer understanding of the condition specifically designated as chronic ulcerative colitis and the realization that there are many ulcerative inflammatory processes of the colon which in the present state of knowledge cannot reasonably be included under this designation have, however, focused the attention of more and more students of this disease on the hypothesis that it is of streptococcal etiology.

A few workers still hold that the condition may be the end stage of an infection by organisms of what used to be called the colon-dysentery group, and which now would include Escherichia coli, Shigella dysenteriae, and Shigella paradysenteriae. Their belief is based on the finding of these microörganisms in a few cases of ulcerative colonic disease, a slightly elevated concentration of antibodies of these organisms in the blood of a few patients and the therapeutic response of some of the patients to administration of antidysentery serum. In study of a large number of patients who have this disease, and in study of another group of patients who have other types of intestinal disorder, including cancer of the colon, infectious granuloma, amebiasis and irritable colon, as well as in study of normal individuals, a similar elevation of the concentration of antibodies of these organisms has been found. Because of these findings, and because men who have held to this belief have selected their cases from regions where the Bacillus dysenteriae is prevalent, this hypothesis of causation would hardly seem tenable.

Another hypothesis of etiology has as its basis the idea of infection by a variety of organisms. The thought has been that many kinds of bacteria, under special conditions, may initiate the pathologic process and may be responsible, in some instances, for its continuance. Among the organisms so incriminated have been Escherichia coli, pneumococci, staphylococci, and others. It has been suggested that the normal intestinal inhabitants assume virulence when bodily defense to infection becomes reduced. The same could be said about any infectious disease, but that would not necessarily permit incrimination of the bacteria present at the site of infection late in the course of the disease.

A third hypothesis of etiology has been concerned with deficiency of vitamins, minerals, and other substances. Studies of large numbers of cases would suggest that when deficiencies occur, they are not primary but occur more as complications of the disease.

Another hypothesis of causation of this disease has been concerned with changes in bodily metabolism, such as occur in diabetes, goiter and similar diseases. Experimental evidence for this is lacking.

Others have explained the condition as the result of a residual infection following infestation by amebas and other parasites. There is much to support the thought that when parasites occur in association with chronic ulcerative colitis, either two separate conditions are present, in which the parasites are causing only part of the symptoms, or they are only incidental intestinal inhabitants.

The most widespread view, and one which is supported by much experimental evidence, is that chronic ulcerative colitis is an infectious disease, caused by a specific microörganism or by a group of microörganisms. The group of microörganisms is of the streptococcal variety and much evidence is at hand to suggest that a diplostreptococcal form of characteristic biologic and morphologic properties is at least one of the main instigators of the disease. In the light of present-day knowledge such an organism must be considered the inciting factor in this disease. Whether or not the organism alone is responsible for the infection, or whether its association with a filtrable virus is important, has been a recent subject of discussion. Some have suggested that the toxin of this organism is alone capable of producing the disease. This thought has led to the search for a filtrable virus. So far, the fact that both the toxin and the organisms seem to play parts in the inception of the infection, again would establish the importance of the presence of the diplostreptococcus.

Men have learned to recognize many factors which predispose to or lay the ground work for the invasion of this organism or its toxins. Among these should be mentioned infections of the upper part of the respiratory tract, such as tonsillitis, bronchitis, and sinusitis; pneumonia; distant foci of infection, particularly teeth with periapical infection; other systemic infectious conditions with intestinal manifestations, including bacillary dysentery and irritable colon; metabolic disturbances including pregnancy; dietary deficiencies and local trauma. These and other conditions seem to render the intestine more vulnerable to the invading organism but many times none of these,

or any other predisposing factors, seems to be at hand, and primary overwhelming invasion by the streptococcus can be demonstrated.

That a disease of such clear-cut clinical symptoms and pathologic signs should call forth a discussion of etiology, and should labor under so indefinite a term as "chronic ulcerative colitis," is unfortunate. Men of large experience in the study of gastro-intestinal problems are thinking of a well-defined entity when they designate an intestinal disease as chronic ulcerative colitis. All admit that the term is sufficiently indefinite to allow the inclusion under it of numerous nondescript conditions, as well as other specific, ulcerative diseases. This is, perhaps, the reason for different opinions on etiology in the past.

Careful analysis of much of the voluminous literature which has accumulated on ulcerative colitis in the last decade demonstrates that there still exists the tendency to classify any kind of colonic ulceration under the designation, "chronic ulcerative colitis." With the accumulation of more exact information on the nature of this most distressing intestinal infection, it has become increasingly apparent that many of the conditions previously thought classifiable under the designation "chronic ulcerative colitis" must be eliminated if the term is to be retained. Those cases in which there are characteristic clinical, sigmoidoscopic, and roentgenologic data represent an entity which should not be confused with other conditions. The history presented by the patients is exactly that which one would expect, judging from the nature of the intestinal pathologic change that is present. There is a diffuse inflammatory process involving the wall of the bowel, and resulting in a characteristic proctoscopic picture and a typical roentgenologic deformity. The nature of the history which the patients will give will depend on the extent of the disease and on the amount of damage to the bowel that has occurred.

All these observations serve to emphasize the importance of a suitable name for the disease now known as "chronic ulcerative colitis." The pathology of the condition, as it is seen in the living and in the dead, has been adequately described. Its sigmoidoscopic picture is clear cut and the steps in its development have been carefully and repeatedly observed and recorded. Its inception seems to have the following sequence: attack of the bowel through the blood stream by a microörganism or its toxin, resulting in multiple thrombosis of capillaries in the wall of the bowel, followed by tiny hemorrhagic infarcts, dissolution of these infarcts, formation of minute abscesses, and the appearance of the disease from the mucosal side as a granular, bleeding surface. Only cases in which this is the pathologic picture should be given a name which represents what is now known as chronic ulcerative colitis.

But since this name readily allows the inclusion of other ulcerative conditions, a more suitable and more descriptive term should be found. To this end many names have been considered and cast aside. The fact that the streptococcus is found to play a part in the picture makes it desirable that this fact be taken into consideration in choosing such a name. However, when etiology is brought into a name, such a name may become cumbersome. A mere description of pathology should be adequate. The designation "thrombo-ulcerative colitis" would be descriptive, clear cut, and would tend to avoid falsely classifying other conditions with this disease.

J. Arnold Bargen.

THE REGULATION OF GASTRIC ACIDITY

THE acidity of gastric contents can conceivably be regulated by several methods, namely (a) neutralization and dilution by alkaline fluid of gastric origin, (b) neutralization and dilution by fluids of extra-gastric origin, including ingested food, and (c) regulation of the production of HCl by the stomach. The first of these methods is admittedly of very minor importance. The mucous secretion of the stomach has an alkalinity of only 0.04 N and is small in volume (1).

The second possibility was emphasized by Boldyreff (2) who originated the theory of the auto-regulation of gastric acidity by regurgitation of alkaline intestinal contents. Since pancreatic juice is the most important component of the intestinal secretion both in point of volume and degree of alkalinity, it would play a prominent role in this mechanism. That regurgitation does occur is generally conceded, but all investigators have not been satisfied that it constitutes a major factor in the regulation of acidity.

The third factor, regulation of acid formation by the stomach, was considered of prime importance by Rosemann (3), who maintained that the acidity of the gastric juice varied with the rate of secretion of the latter. This alteration of the acidity was accomplished by the parietal cell, which Rosemann believed was able to convert into HCl a variable proportion of the NaCl passing through it. This theory has suffered considerably under the attack of recent investigators, who have adduced evidence favoring the view that the secretion of the parietal cell is a pure solution of HCl of a constant concentration (approximately 170 MM. or clinical units) (4, 5, 6, 7). These authors maintain that the variations in the acidity of pure gastric juice are due to the dilution and neutralization which results when variable quantities of this acid solution are secreted and mixed with a relatively constant quantity of another fluid consisting of mucus, sodium chloride, and buffers. This alkaline fluid is of such small volume as to significantly effect the acidity of gastric juice only when the rate of production of acid is very small. Since the acidity of gastric juice as normally secreted is much higher (0.4-0.5%) than that of normal gastric contents (0.2%), the question arises as to how the latter is maintained at this figure, if regurgitation is not the major factor.

During the greater portion of the digestive period, the enormous diluting and buffering power of a normal meal will, of course, prevent the acidity from rising very high. But what prevents the acidity from eventually becoming excessive? A significant new possibility is suggested by the work of Wilhelmj, McCarthy and Hill (8), Griffiths (9), Day and Webster (10) and Crider and Thomas (11), all of whom have observed that the introduction of HCl in the duodenum will depress the further secretion of acid by the stomach. This would provide a truly automatic mechanism for the regulation of gastric acidity.

A combination of the above acid inhibition and intestinal regurgitation mechanisms, offers a most attractive compromise theory, which may be considered to operate as follows. When the acidity of the chyme entering the duodenum becomes too high, the further

production of HCl is inhibited. At the same time the acid acting from the duodenum inhibits gastric motility, relaxing both the pyloric antrum and sphincter (12). This permits regurgitation of alkaline fluids from the intestine, which results in a rapid diminution in the acidity of the gastric contents. It would seem that both processes are important, for, in the absence of regurgitation, the secretion of a greatly reduced quantity of juice of an equally reduced acidity could only very slowly accomplish a significant reduction of the acidity of the whole gastric contents, and until the acidity was restored to normal, the acid acting from the duodenum would markedly retard evacuation. On the other hand, if acid secretion continued unabated, the volume of intestinal fluids being regurgitated into the stomach would have to be almost as great as the volume of gastric juice being secreted into the stomach, a condition which would also interfere with gastric evacuation. However, by a proper coordination of the two processes, namely, inhibition of acid production and neutralization by regurgitation, the regulation of gastric acidity could be most efficiently accomplished.

It would be of interest to know whether the mechanism by which acid in the duodenum inhibits gastric secretion is reflex or humoral in nature. It would also be of importance to determine whether a disturbance in this process is responsible for clinical hypersecretion.

John S. Gray.

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Book Review

Clinical allergy, manifestations, diagnosis and treatment. By A. H. Rowe. Philadelphia, Lea and Febiger, 1937, 812 pages.

THIS book should be of great interest to all physicians who see many patients with gastro-intestinal disease. Rowe has done much pioneering in the field of food sensitiveness and he here sums up in very readable form the wisdom which has come to him during the years. In addition he gives the student easy access to a large literature.

Those gastro-enterologists who are using Rowe's elimination diets will be interested to see the modifications that he has made in them. They are particularly useful in cases of migraine in which the diet may have to be continued for some time in order to tell whether or not the attacks are going to disappear.

Some readers may disagree with Rowe's view that ordinarily one must keep up the diet for weeks or a month or more before one can tell whether or not it is doing any good. The reviewer's impression is that ordinarily, at least in cases of indigestion, abdominal pain and soreness, if the relief does not come in twenty-four hours, it is not going to come with the particular elimination diet being used.

Many physicians will doubtless find helpful Rowe's instruction for the taking of histories. The questionnaire which begins on page 664 should be very useful.

It is nice to find Rowe stating now that in many cases the skin tests are of little help, especially in the diagnosis of food sensitiveness.

We are particularly pleased to see the large number of recipes for the preparation of food. They should be very helpful particularly to mothers who have to cater to children with marked sensitiveness to milk, eggs, and other commonly used foods.

On page 170 Rowe wisely points out that the enthusiastic allergist must always remember that many of his patients, and even those who have definite allergic symptoms may be suffering mainly from nervous complaints, and they may be markedly psychopathic or "relatives of the insane." Unfortunately the markedly allergic person is commonly tense and nervous and hypersensitive to everything, and the handling of his problems calls for a tremendous amount of skill, understanding, and patience on the part of the physician.

Certainly Rowe's book should be owned and read and consulted frequently by every busy clinician. There is no question that as civilization advances, and man has to come in contact with more hundreds of substances gathered from the four corners of the world, there will be more cases of allergic disease, and physicians will always have to keep thinking of this type of sensitiveness as a possible cause of illness. Allergic sensitiveness is now being found to explain some common and very annoying symptoms such as canker sores in the mouth for which there was formerly no explanation and no useful or logical treatment.

About the only suggestion that a reviewer might make for future editions of this book is that Dr. Rowe then base his statements more on his own experience and less on the statements which he finds in the literature.

Walter C. Alvarez, Rochester, Minn.

Abstracts

SEYMOUR, WILLIAM B. AND LIEBOW, AVERILL A.

"Abdominal Intermittent Claudication" and Narrowing of the Celiac and Mesenteric Arteries. Ann. Int. Med. Vol. X, pp. 1033-1041.

The correlation of the clinical and pathological data of a case of gradual occlusion of the celiac, mesenteric and left iliac arteries is presented by the authors.

A spinster of 76 was admitted to the medical ward complaining chiefly of abdominal pain after eating. Numbness in the left calf upon exertion, tingling sensations in the fingers, and constant tinnitus had been noticed for six months. The abdominal pain began three months before admission. Immediately upon the ingestion of any food except water and fruit juices there would appear a sharp steady pain in the region of the umbilicus radiating to the symphysis pubes, left lower quadrant and back. The pains would last 5 to 30 minutes and were followed by a constant slight dull ache in the epigastrium. On two occasions she had been nauseated and had vomited a thin colorless fluid. One week before admission she had had a watery diarrhea of two days duration. She thought her stools had been black at times. There had been no abdominal distention.

Physical examination revealed marked arteriosclerosis of the retinal vessels and the arteries of the extremities. The left lower extremity was cooler than the right, and the blood pressure and pulse were unobtainable in it. In the region between the umbilicus and mid-epigastrium just to the left of the vertebral column a firm, but vaguely defined, immovable, pulsating mass was felt.

A positive guaiac test of the stools and a leucocytosis of 13,000 was found. A gastro-intestinal X-ray series showed atony of the stomach with 15% retention of the gastric contents in six hours, and motor delay throughout the small intestine.

Nine days after admission the patient vomited 300 c.c. of coffee ground material which was weakly positive for guaiac. Exploratory laparotomy was performed at which nothing of particular note was found. Eighteen hours later the patient died.

At postmortem the entire gastro-intestinal tract was distended with dark red, malodorous fluid. A loop of ileum adherent to the posterior wall of the bladder was almost black, and so soft it tore easily upon an attempt to loosen it. Microscopically the mucosa of the small intestine had undergone complete necrosis. The aorta showed marked atheromatous change with ulceration and calcification. About the mouth of the celiac axis was deposited a rosette of very hard material which virtually obliterated the ostium. The mouth of the superior mesenteric artery likewise was narrowed to an opening of pinpoint size by a hard incrustation in its wall. A firm, fresh, laminated, red and gray thrombus completely obstructed the proximal 5 cm. of the vessel. The lumina of the left common and external iliac arteries were reduced to mere crescentic slits because of tremendous thickening of the intima. A fresh thrombus partially occluded the left common iliac artery. The heart showed considerable atherosclerosis of the coronary vessels, but no occlusion.

Accompanying this report is a tabular summary including those cases in the literature of abdominal pain associated with vascular disease in which the findings at necropsy are stated.

B. B. Vincent Lyon and
C. W. Wirts, Jr., Philadelphia.

RAWLES, WILLIAM B., WEISS, SAMUEL AND COLLINS, VERA L.

Liver Function in Rheumatoid (Chronic Infectious) Arthritis: Preliminary Report. Ann. Int. Med., Vol. X, pp. 1021-1027, Jan., 1937.

One hundred patients were studied to determine whether any disturbed liver function occurred during the toxemia of rheumatoid (chronic infectious) arthritis. The Azorubin S test was selected for the liver function test, which is performed in the following manner. The duodenal tube is passed in the morning on a fasting stomach. When the tube reaches the duodenum and a yellowish-brown bile begins to flow 1.0 c.c. of 1.0 per cent solution of Azorubin S is injected intravenously. Five minutes after the injection of the dye 40 c.c. of a 25% magnesium sulphate solution is injected through the duodenal tube. In normal individuals a characteristic, deep red bile appears about 17 minutes after injection of the dye. From 15 to 30 minutes was accepted as the normal appearance time of the dye. Less than 15 minutes and more than 30 minutes indicated liver dysfunction in proportion to the decreased or increased appearance time of the dye.

In analyzing the 100 cases the authors report that in four cases the appearance time was less than 10 minutes; in 32 it was 10 to 15 minutes; in 45, 15 to 30 minutes; in four, 30 to 35 minutes; in nine, 35 to 40 minutes and in six, over 40 minutes. Of the entire number studied 55 per cent showed some liver dysfunction.

From these figures, although it appears that liver dysfunction is parallel to the severity of the disease, there was no relation between the duration of the disease and the liver function. A quantitative determination of serum proteins was made in patients showing liver dysfunction and in most cases, there was a slight reduction of the total serum protein and a reversal of the albumin-globulin ratio. In the majority of cases studied, there was a correlation between liver dysfunction, the reduction of serum proteins and reversal of the albumin-globulin ration.

The authors conclude that liver dysfunction as determined by the rate of excretion of Azorubin S, was present in 55% of 100 patients with rheumatoid arthritis and that it occurred with greater frequency in patients with a severe than with a mild form of the disease.

The interpretation of liver dysfunction in patients with a *decreased* appearance time is based upon the findings of Whipple, Peightal and Clark who reported a hypersecretion of phenoltetrachlorphthalein with small doses of phosphorus which they attributed to the irritative effect of the phosphorus on the parenchyma of the liver. Whether this irritative effect can also be attributed to the Azorubin S, in the reviewers opinion, merely is conjectural without further substantive proof. If this opinion is correct, it would materially alter the results of the 100 cases studied by the authors, reducing their evidence of liver dysfunction in rheumatoid arthritis from 55 per cent to 19 per cent.

B. B. Vincent Lyon and
C. W. Wirts, Jr., Philadelphia.

KANTOR, JOHN L. AND COOPER, LENNA F.

The Dietetic Treatment of Constipation with Special Reference to Food Fiber. Ann. Int. Med., Vol. X, pp. 965-978, Jan., 1937.

The thesis of this paper is that constipation should be treated as thoroughly as possible by diet before calling upon artificial products for assistance. For this reason, and because of their recognized superior laxative properties, fruits were selected as the subject of this study. Cowgill has laid down the general procedure for the study of laxative substances on a fiber-equivalent basis, and has suggested that for normal men the physiological fiber minimum for adequate laxation corresponds to a daily intake of 90 to 100 milligrams of fiber per kilogram of body weight. This experiment was

planned, therefore, to determine the relative usefulness of three fruits (prunes, apples and bananas) on a fiber-equivalent basis.

The subjects selected for this study were nine hospital dietetians. The experiment was divided into eight periods of at least nine days each; in the first period the diet was uncontrolled while in the seven following periods there was a variation of fiber content and combination.

The laxation (number of stools) were recorded for each day of every period by each subject. In this paper the laxation is expressed in terms of stools per week per person.

The total colon emptying time was observed roentgenographically in five of the subjects during the first six periods of the experiment.

The normal total colon emptying time was determined from a review of 844 private patients. It was found to be 72 hours.

The weight of the stools was determined in the last two periods by actual measurement immediately after passage.

Experimental Conclusions: According to the average laxation and colon emptying time, the laxative power of the three fruits when tested on a strictly fiber-equivalent basis (66 mg. per kg.) may be rated as follows: First, prunes with laxation of 7.7 and colon emptying time of 91 hours; second, bananas, with laxation of 6.8 and colon emptying time of 98 hours; third, apples, with laxation of 6.1 and colon emptying time of 115 hours.

It is probable that the simultaneous employment of several sources of fiber is superior to the use of a single variety. This is suggested by the fact that laxation was freer in the preliminary period of this experiment when the sources of fiber were more freely chosen than in most of the subsequent periods when the sources were restricted.

Clinical applications: Accompanying this article are three tables showing the fiber component of fruit, vegetables and cereals not only as a percentage, but as it occurs in the average serving portion.

According to the Cowgill standard of 100 milligrams of fiber per kg. body weight, a man of 70 kg. will normally require 7 gm. of fiber daily. The exact procedure of selection may be outlined as follows:

1. From the list of fruits, three varieties may be chosen, preferably one for each meal. Assuming that apples, prunes and bananas are taken, it will be noted that the fiber in the average portions adds up to 2.2 gms. (1.0 gm. plus 0.6 gm. plus 0.6 gm.).

2. Four vegetables should be selected including one serving of potato (0.4 gm.). If to this are added string beans (1.05 gm.), spinach (0.45 gm.) and asparagus (0.35 gm.) the total from this source becomes 2.25 gm.

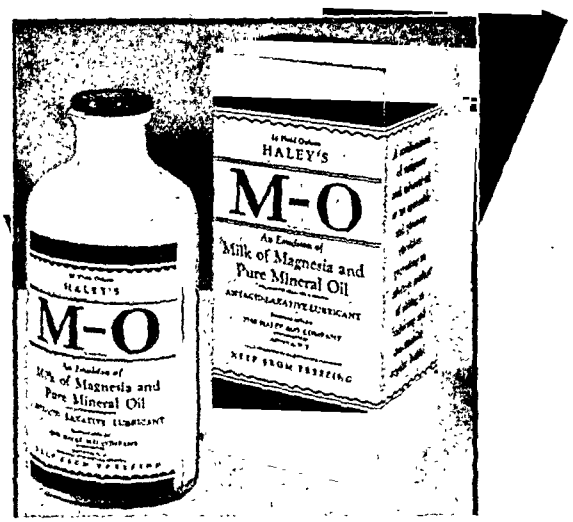
3. For the cereal food stuffs one whole grain cereal such as shredded wheat (0.78 gm.) with perhaps a slice of whole wheat bread (0.36 gm.) should be taken for breakfast. At each of the other two meals two slices of bread (0.72 gm.) may be used. The foods used in the example give a daily total of 7.03 gm. of fiber.

The authors conclude that an adequate fiber intake is important in the dietetic treatment of constipation. This fiber is supplied by three classes of foodstuffs — fruits, vegetables and cereals.

With the aid of the data furnished in the fiber-content tables, constipation diets may be planned on a quantitative basis.

For the relief of many, if not most cases of simple constipation, ordinary servings of fruit should be taken three times daily, preferably as deserts. It is suggested that the daily use of ap-

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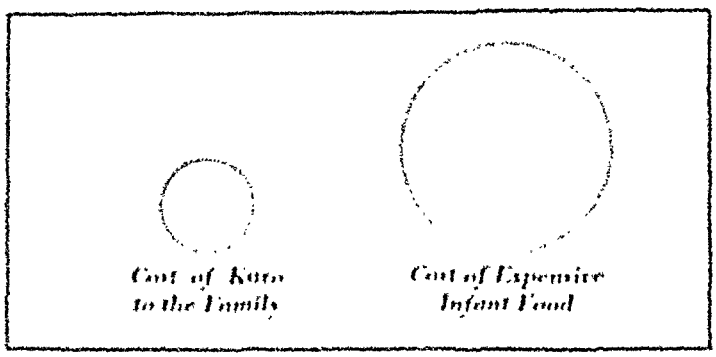
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proximately 2 gm. of fruit fiber in addition to the "average" diet containing four vegetables and some whole grain foodstuffs, suffices in such cases. This amount would be supplied for example by six prunes, one banana and one medium-sized apple.

B. B. Vincent Lyon and
C. W. Wirts, Jr., Philadelphia.

RANKIN, F. W. AND GRAHAM, A. S.

Closure of Colostomy. S. G. O., Vol. 64, No. 1, pp. 59-62, Jan., 1937.

In the experience of the authors more than one-half of the cases in which obstructive or exteriorization type of colon resection was done the colostomy closed spontaneously after a period of from 6 weeks to two months. Failure of the colostomy to close may be due to spur formation, attachment of the mucosa to the skin edges, or to obstruction beyond the colostomy.

The preparation of the patient for insertion of clamps should be as elaborate as that for the primary resection. The author uses long curved Kelly forceps which are inserted and closed to the first notch. Each subsequent day the clamps are tightened one notch. Usually the septum is cut through in 5-6 days, but occasionally a forcep will hang on for 8-9 days. It should never be pulled out—they should be allowed to fall out.

In closing the colostomy an elliptical incision is made through the skin, around the stoma down to the fascia. The index and middle fingers are now inserted into the two ends of the bowel, using them as retractors. The dissection is now carried down to the peritoneum on all sides. The margin of skin which has been left on the ends of the bowel are cut away and the stoma closed with two rows of chromic catgut sutures places transversely. A third row of sutures may be used if there is ample room, or it seems necessary. Any disparity between the size of the two segments of bowel may be overcome by splitting the wall of the smaller one. After flushing out the wound with saline and later ether, the fascia is closed by interrupted sutures. The skin edges are loosely approximated and rubber tissue drains are inserted down to the fascia. The percentage of closure by primary union is remarkably high.

Three figures accompany the article.

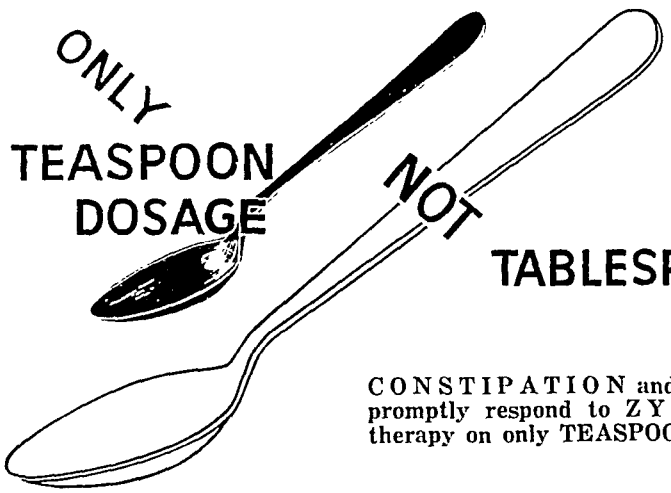
In discussing the transformation of gastric ulcer into gastric carcinoma the authors feel that the criteria by which such a diagnosis is arrived at are very difficult to evaluate. From their observations in the Gastro-Enterological Clinic of the Fourth Medical and Surgical Divisions of Bellevue Hospital during the last eight years they are obliged to question whether a gastric ulcer ever becomes malignant.

They reviewed 118 cases with carcinoma of the stomach. The diagnosis seemed quite certain. The average age of the patients was 56.7 years; 83 per cent were males. The average duration of symptoms was 45.3 weeks. In a review of 104 cases of gastric ulcer the average age of the patients was 47 years; 88% were males. The average duration of symptoms was 6 years. In this group of gastric ulcers 17 per cent were in the pyloric region—the region in which Holmes and Hampton thought carcinomatous degeneration most apt to occur. Those cases have been followed on the average of 15 months and the authors feel that they run no risk of carcinomatous degeneration.

The author concludes that once a gastric ulcer always a gastric ulcer, but realizing that in an occasional case it is difficult to determine whether the lesion is a true benign ulcer or an early ulcerating carcinoma. Questionable cases, which should not constitute over 7 to 8 per cent of those coming under one's observation, should be submitted to resection.

N. M. Percy, Chicago.

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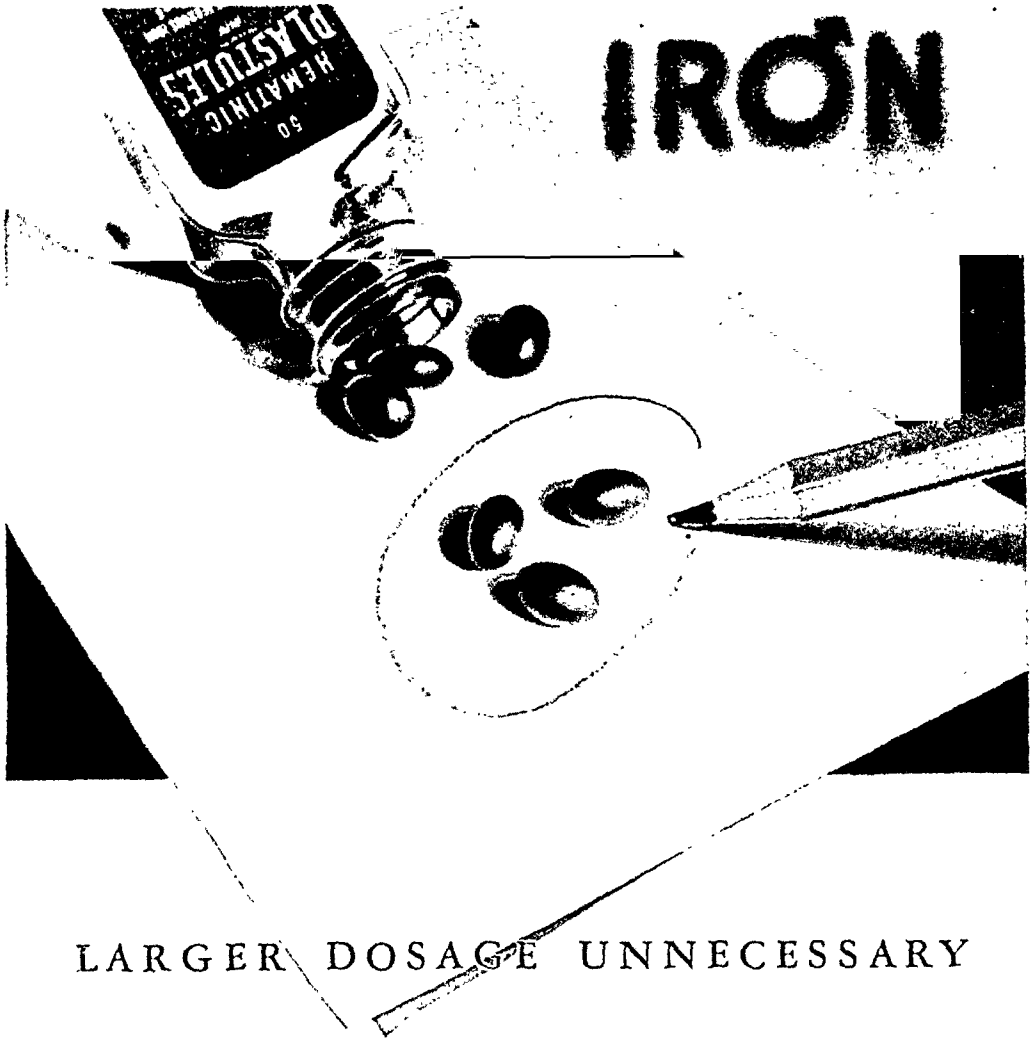
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HINTON, J. W. AND TRUBEK, M.

The Transformation of Gastric Ulcers into Gastric Carcinoma. S. G. O., Vol. 64, No. 1, pp. 16-21, Jan., 1937.

At the Central Emergency Hospital in Moscow the author has treated 426 patients with acute perforated ulcers during the period for 1933 and 1934. Less than two per cent of the patients were women. According to decades the greatest number occurred between the ages of 31 to 40; next in order of frequency of cases was the age group from 21 to 30. The number of perforated gastric ulcers increased with each decade up to the 5th, in which it outnumbered the perforations of duodenal ulcers. The greatest number of perforations occurred during the spring. The number during the summer, autumn and winter was about the same.

Because the incidence of cure of duodenal ulcer by gastric jejunostomy fell to 50 per cent when the patients were examined ten years after operation, and because those patients later were so frequently subjected to a radical gastrectomy under difficult conditions, and because of the high incidence of gastrojejunal ulcer after operation, the author has been convinced that primary partial gastrectomy with removal of the upper part of the duodenum in the majority of cases is the treatment of choice. In elderly or debilitated patients with extensive peritonitis, simple suture of the ulcer with gastro-enterostomy is done.

The type of resection employed is the Billroth I in about 80 per cent of the cases; the Polya-Balfour in about 20 per cent. The mortality from the resection cases in 1933 was 8.5 per cent in 210 cases. In 1934 it was 6.6 per cent in 121 cases. The mortality for all operated cases was 12.8 per cent.

Four figures accompany the article.

N. M. Percy, Chicago.

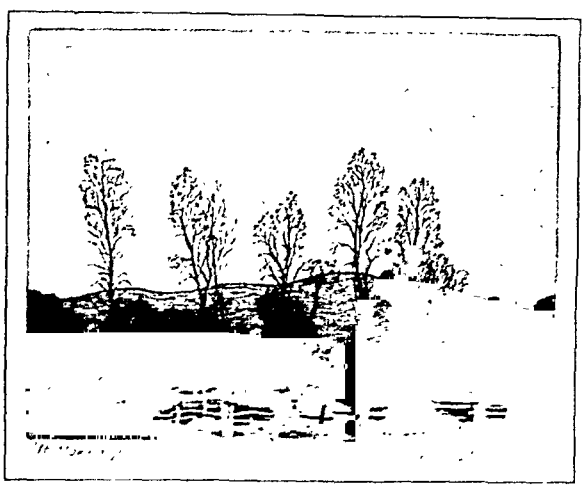
SANDWEISS, DAVID J.

Dietetic, Parenteral and Surgical Treatment in Peptic Ulcer. J. A. M. A., Vol. 108, p. 700, Feb. 27, 1937.

This report is based on observations made on 291 patients with peptic ulcer who were treated during 1,019 attacks. This group varied in age from fourteen to seventy-four years, consisted of both sexes and was made up of both private and clinic cases. They were divided into two groups: acute, or those with ulcer symptoms for less than five years; and chronic, or those with ulcer symptoms for more than five years.

The author found that approximately 90 per cent of private patients became symptom free with the dietetic-alkali management, and 75 per cent of the clinic ones. Of those who did not respond to the diet-alkali regimen, approximately 60 per cent became symptom free after injections of stock vaccine, larostidin or synodol. In twenty-two patients, distilled water was injected with comparable results. The author believes that the beneficial results obtained with the parenteral treatment were due to the psychic effect, not any intrinsic something in the material used. Some patients did not respond to any form of treatment, but when relieved of stresses and strains they became symptom free. Most of the patients in this series returned with recurrences, the period of remission being shortest in those treated by parenteral methods. This was probably due to the fact that the diet was not controlled as well in these cases.

It is believed that the diet should be restricted during the symptom free intervals as well as during recurrences. Of 155 patients treated medically and surgically, there were only five who were symptom free at the end of five years. The author believes that the parenteral method is indicated only in those cases which do not respond to diet and surgery, only where complications are present. At the present time, all one can hope to do is to relieve symptoms, delay relapses and pre-



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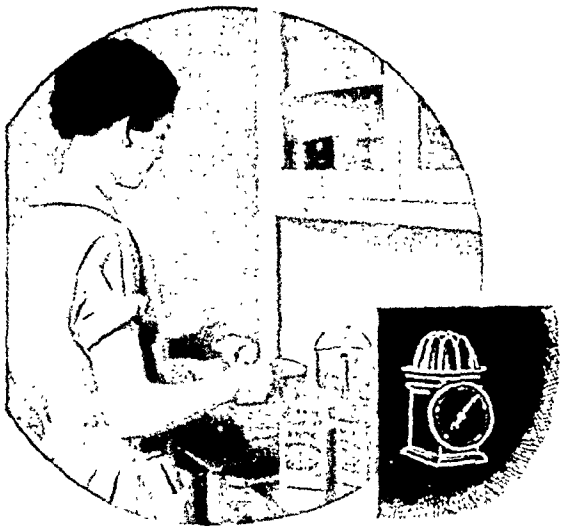
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½ cup hot water					
½ teasp. salt					
½ teasp. whole mixed spices					
1 env. Knox Sparkling Gelatine	7	6			
¼ cup cold water					
¾ cup tomatoes strained	150	2		6	
2 tablespoonfuls vinegar					
½ cup chopped cabbage	50	1		3	
½ cup chopped celery	60	1		2	
¼ cup canned green peas	40	1		4	
¼ cup cooked carrots cubed	40			4	
Total		11		19	120
One serving		2		3	20

Bring hot water, salt and spices to a boil. Pour cold water in bowl and sprinkle gelatine on top of water. Add to hot liquid and stir until dissolved. Strain into tomatoes and stir in vinegar. Chill until almost set, then add vegetables. Mold and chill until firm. Serve on lettuce with or without dressing.

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OPPENHEIMER, GORDON D., GLASS, AMEIL AND NETTER, FRANK.

Status of Cholecystogastrostomy in Obstructive Jaundice. J. A. M. A., Vol. 108, p. 707, Feb. 27, 1937.

A study was made of thirty-four patients on whom a diagnosis of carcinoma of the head of the pancreas, the common bile duct or the ampulla of Vater had been made. After laparotomy, a diagnosis of carcinoma of the head of the pancreas was made in thirty cases. All patients had a cholecystogastrostomy done except one who had a choledochoduodenostomy done. In all cases, the gall bladder was tense or distended.

"Of the thirty cases diagnosed as carcinoma of the head of the pancreas at operation, all with the exception of five were found to show this condition, or carcinoma of the common bile duct below the cystic duct or carcinoma of the ampulla of Vater. These five cases presented the following conditions: (1) cirrhosis of the liver, (2) subacute yellow atrophy, (3) carcinoma of the stomach with liver metastasis, (4) hepatosplenomegally, and, (5) chronic pancreatitis. The operation of cholecystogastrostomy was probably not indicated in the first four of the aforementioned cases."

Within the past year punch biopsies or small incisional biopsies have been done with the idea that early cases may be treated by a two stage operation.

The operative mortality was 41.3 per cent, while seventeen of nineteen patients discharged were known to be dead in three to twelve months after operation.

The author believes this operation is indicated in those cases in which there is a nonremovable obstructive lesion of the common bile duct below the cystic duct. It is also indicated in carcinoma of the pancreas or the ampulla as a palliative measure.

Francis D. Murphy, Milwaukee.

SMITH, FERRIS.

Lipoma of the Tongue. J. A. M. A., Vol. 108, p. 522, Feb. 13, 1937.

Lipoma of the tongue is a very rare condition, there being forty-four authentic cases in the literature. It has been found to occur at almost any age, some of the cases being congenital and appearing shortly after birth. It is more frequent in the male when a pure lipoma, but more frequent in the female when a fibro-lipoma. It may originate from the small masses of fat in the genioglossus muscle, in the preepiglottic fat or by a metaplasia of the connective tissue which separates the muscle bundles. The tumor is benign, the size varying from that of a grain of rice upward, and is usually located on the edge of the tongue and may be submucous, interstitional or intermuscular. The author reports a case of seventeen years duration which was cured by surgical removal of the growth.

Francis D. Murphy, Milwaukee.

DAY, P. F. AND DARBY, W. J.

Inverse Relation Between Growth and Incidence of Cataract. J. Nutrit., Vol. 12, 387, 1936.

Day and Darby gave 200 young rats a diet deficient in vitamin G. After a period of two weeks, daily supplement of vitamin-containing foods were given to all except a control group; 86 per cent of the controls developed cataract. The animals receiving vitamin supplement were grouped according to growth, and an inverse relationship between growth and cataract appeared. That is, the greater the growth, the lower was the incidence of cataract. Only a small amount of the vitamin was required to prevent cataract.

BOLKER, HERMAN, JACOBI, MENDEL AND KOVEN, MORRIS T.

Primary Carcinoma of the Liver with Bone Metastasis. Ann. of Inter. Med., Vol. 10, pp. 1212-1221, Feb., 1937.

A search of the literature only revealed nine cases of primary carcinoma of the liver with bone metastases. These nine reported cases are listed together with a detailed report of the history, physical and laboratory findings and autopsy findings of the authors' case.

The tumor from the authors' case is a parenchymal hepatoma, similar in gross appearance to several of those previously reported, though it did not occur in a previously cirrhotic liver. It is the only case with bone metastases in a woman, and occurred at 29 years of age, while seven of the nine others occurred in patients over 45 years of age. Characteristic extensive vascular invasion and bile production in the metastases were present. Metastases in the lung bed were not found after extensive search, which suggests a specific affinity of the neoplastic cells for the bone marrow in these cases.

The origin of this type of neoplasm is probably in the benign adenoma whether this be of the congenital type, or due to proliferation in the parenchyma distorted by cirrhotic change.

The tumor acts like an organ rather than tissue in its metastases and it is suggested that the metastases might have the physiologic activity of the original organ.

The authors call attention to the liver as a focus for metastatic bone neoplasm *in obscure* cases.

B. B. Vincent Lyon and
C. W. Wirts, Jr., Philadelphia.

PROTECTION OF VITAMIN C IN CANNED FOODS AGAINST ENZYMATIC DESTRUCTION

• One of the unusual features of modern food preservation by canning is the high degree of protection afforded vitamin C during the canning procedure. Of all the vitamins, C is probably the most readily destroyed. Spinach, for example, will lose one-half its vitamin C content upon standing three days at room temperature and practically all of its antiscorbutic potency in seven days' time (1).

Oxidation is the principal factor operating in the destruction of vitamin C. The rate of oxidation depends—among other things—upon temperature, degree of exposure to oxygen, and presence of substances which catalyze the oxidation reaction. Chief among the catalysts is the enzyme known as ascorbic acid oxidase. This enzyme is instrumental in the loss of physiologically active forms of cevitamic acid (ascorbic acid) by catalyzing the transformation of this latter substance into dehydrocevitamic acid (dehydroascorbic acid), which is more readily decomposed by a nonenzymic reaction into a compound having no anti-scorbutic activity. This enzyme is apparently widely distributed in the vegetable kingdom, having been found in cabbage, carrots, lima beans, parsnips, peas, pumpkin, spinach, squash, string beans, sweet corn and swiss chard. Fortunately, the cevitamic acid oxidase is completely inactivated by heating to 100°C. for one minute (2).

In modern canning practice field crops are harvested at the optimum stage of maturity and canned as rapidly as possible—usually within a few hours' time. Early in every canning procedure the product receives either a blanch or a pre-cook or exhaust, the primary purpose of which is to drive out air from biological tissues and to establish a vacuum by expanding the contents of the can by heat, contraction upon cooling resulting in a partial vacuum within the can. These preliminary heat treatments together with the heat process serve both to destroy oxidative enzymes and to remove most of the air from the can.

Thus, the various practices in the canning procedure combine to afford excellent protection for this most labile accessory food factor known as vitamin C.

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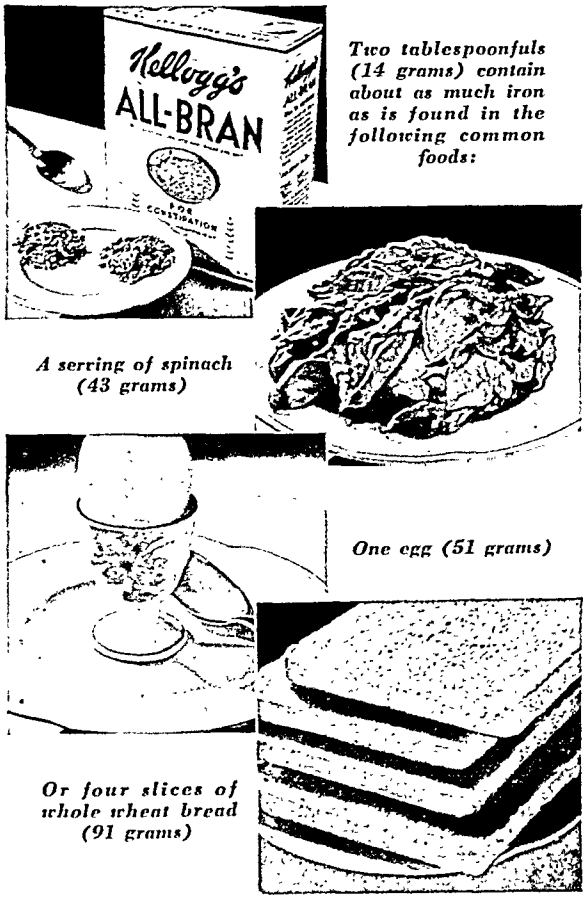
(1) 1935, Food Research, 1, 1 (2) 1936, J. Biol. Chem., 116, 71

This is the twenty-seventh in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.



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ALT, HOWARD L. AND SWANK, RAY L.

Thrombopenic Purpura Associated with Catarrhal Jaundice: Report of a case. Ann. Int. Med., Vol. 10, pp. 1049-1053, Jan., 1937.

A patient has been observed in whom an acute thrombopenic purpura occurred simultaneously with an acute catarrhal jaundice.

A male, age 24, was admitted to the hospital complaining of malaise, epistaxis and jaundice which followed an upper respiratory infection one month before, and the gradual development of anorexia, muscular aching, constipation, discomfort in abdomen, highly pigmented urine, lighter colored stools and petechial spots for three days prior.

The significant laboratory data show an absence of blood platelets; no clot retraction; increased bleeding time; 3+ bile in the urine; a strongly positive benzidine test for occult blood in feces and in urine; increased quantitative van den Bergh; increased icterus index and a marked increased dye retention on functionally testing the liver. On duodenal intubation and administration of 100 c.c. of magnesium sulphate, a thin greenish mucoid secretion was obtained.

The patient was treated by transfusion of citrated blood and an injection of whole blood. Subsequently calcium gluconate, viosterol, and liver extract were given each day. He became entirely well and was discharged from the hospital three weeks after admission. There has been no recurrence of symptoms one and one-half years after the illness occurred.

Accompanying this report is a discussion of the etiologic relationship between thrombopenic purpura and catarrhal jaundice. Also evidence is presented which suggests a relationship between thrombopenia and liver disease.

B. B. Vincent Lyon and C. W. Wirts, Jr., Philadelphia.

SIXTEENTH ANNUAL SESSION AMERICAN CONGRESS OF PHYSICAL THERAPY TO BE HELD IN CINCINNATI IN SEPTEMBER

Cincinnati and its medical groups will be host to the American Congress of Physical Therapy which meets at Netherland Plaza Hotel, Cincinnati, September 20 to 24, 1937.

Never before has there been such interest and enthusiasm for an annual session as is being displayed this year for the September meeting. Plans are being made for a very large attendance which will be comfortably cared for at the Netherland Plaza Hotel.

Of special interest is the scientific program with its diversified symposia, clinical conference groups, demonstration clinics and sectional meetings. Every specialty in medicine and surgery will be adequately represented. The Scientific exhibits will be extensive and varied and should comprise an important part of the entire session. The technical exhibits will prove profitable in information to those who seek familiarity with the newer apparatus and equipment in physical therapy.

From every standpoint the 16th annual session offers an intensive "refresher" course in which will be embraced subjects like short wave diathermy, ultraviolet radiation, low voltage currents, exercise, massage, etc. Featured symposia include fractures, vascular diseases, poliomyelitis, fever therapy. There will be no registration fee but the meeting is open only to duly licensed physicians and properly vouched for technical assistants. Plan now to attend the Congress session in September.

A. R. Hollander, Executive Director,
30 N. Michigan Ave., Chicago, Ill.

A second book containing scientific facts on commercially canned foods has recently been published by the American Can Company, compiled by the Nutrition Labo-

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Recent reports on the use of Sulfanilamide in gonococcal infections are so encouraging as to suggest that a chemotherapeutic specific has been found for this type of infection also.

Tablets Sulfanilamide, Lilly, 5 grains (0.325 Gm.) are supplied in packages of 40, 100, and 500.

ELI LILLY AND COMPANY

Principal Offices and Laboratories, Indianapolis, Indiana, U. S. A.

ratory in the Research Department of the Company. The book, NUTRITIVE ASPECTS OF CANNED FOODS, has been prepared for doctors and scientific workers with canned foods. The earlier book, FACTS ABOUT COMMERCIALLY CANNED FOODS, was published last year.

The book is a general summary of facts about tin containers and canned foods. It is divided into two sections. The first deals with the preservation of foods, dietary requirements, the mineral and vitamin conservation in canned foods, infant nutrition, and the safety of canned foods under modern methods of packing. Section two takes up the manufacture of the cans, including the tinplating, enameling, and a description of can sizes. It also discusses the canning procedure from the raw materials through the sealing of the cans and the heat processing.

The back of the book contains an appendix of reference tables of all kinds. There are charts on human energy expenditures, dietary requirements, mineral and iodine content of various foods, and analyses of canned foods of many kinds. A bibliography contains an appendix of references to the more complete works on each phase of the industry as well as the general texts used in preparation of the book.

SUMMER DIARRHEA IN BABIES

Case C (calcium caseinate), which is almost wholly a combination of protein and calcium, offers a quickly effective method of treating all types of diarrhea, both in bottle-fed and breast-fed infants. For the former, the carbohydrate is temporarily omitted from the 24-hour formula and replaced with 8 level tablespoonfuls of Casec. Within a day or two the diarrhea will usually be arrested, and carbohydrate in the form of Dextri-Maltose may safely be added to the formula and the Casec gradually eliminated. Three to six teaspoonfuls of a thin paste of Casec and water, given before each nursing, is well indicated for loose stools in breast-fed babies. Please send for samples to Mead Johnson & Company, Evansville, Indiana.

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"CONNOTATIONS"

Thomas Vicory, wrote in 1577, "The Chirurgeon must know the anatomie for all authors write against those surgeons that work in man's body not knowing the anatomie; for they be likened to a blind man that cutteth in a vine tree, for he taketh away more or less than he ought to do."

Our present knowledge of carcinoma of the gall bladder, except for detailed histologic studies is derived from the writings of Musser (1890), and Ames (1894).

Maxon, in 1868, reported a villous carcinoma of the gall bladder in a male child four years of age. Numerous writers refer to this unusual case. Maxon in his report, did not mention the age, although he did state that the patient was intemperate and a brush maker by trade.

Chaufford, in 1899, stated, "there is no disease of the gall bladder and ducts; the only disease is that of the liver cells themselves."

Glisson, in 1861, intimated that a sphincter of the common bile duct existed. In 1887, Oddi in an attempt to explain the cause of dilatation of the biliary tree observed and described the sphincter in both man and animals. Gage an anatomist described the sphincteric arrangement of the muscle fibers in 1879.

Brown-Sequard reported to the Societe de Biologi in Paris. June 1, 1889, the effect of subcutaneous injections of an extract of the testes which resulted in a remarkable increase of physical and mental powers. The subject was 72 years of age and oddly he himself was the patient. He is credited as having laid the foundation in theory and in clinical practice of the doctrine of internal secretion.

As early as 1797, Saunders stated because of the oblique manner in which the common duct traversed the duodenal portion of the intestinal its method of emptying is influenced by intestinal peristalsis. Concerning this observation much experimental work has been done and yet this question remains unsolved.

Comparison of the calcium content of liver bile and gall bladder, bile was first reported by Hoppe-Seyler in 1878.

The first case of displaced epiphysis of the femur was recognized by Brousseau in 1867. This was an accidental postmortem finding in a boy aged fifteen, who had received his fatal injury when a bicycle passed over his hip joint.

H. J. Sims, Denver.

CHEMICAL NATURE OF VITAMIN E ESTABLISHED

Important progress in establishing the chemical structure of vitamin E has been made by Dr. E. Fernholz at the Merck Research Laboratories, according to a statement issued recently by George W. Merck, President of Merck & Co., Inc., Rahway, N. J.

The work was undertaken at the suggestion of Dr. Herbert M. Evans of the Institute of Experimental Biology at the University of California, where much of the original work on the isolation of vitamin E and the investigation of its biological activity has been done in recent years. A report of this work by Dr. Fernholz has just appeared in the Journal of the American Chemical Society for June.

The work of Evans and his collaborators, starting in 1927, on the specific relation between a form of "habitual

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When constipation occurs as a result of special restricted dietaries, Mucilose supplies the bland *hemicellulose* (vegetable gum) which, according to Williams and Olmsted meets the deficiency.

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*Williams, Ray D., and Olmsted, W. H.: Ann. Int. Med. *10:* 717 (Dec.) 1936.

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The sodium glycocholate and taurocholate, the salts of conjugated colic acids in their native association as separated from fresh ox gall.

A stable dry powder; uniform in composition; efficient for the well known therapeutic uses of ox-gall—in disorders due to faulty bile functioning.

Bile Salts preferably to be dispensed in capsule by itself, or in combinations in powder.

Offered in powder, ¼ oz., 1 oz. vials; in capsules, each three grains Bile Salts.

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abortion" in lower animals and a deficiency in the diet, has demonstrated the presence of vitamin E in wheat germ, cottonseed and palm oils, and in lettuce. The lack of this vitamin in the diet of rats leads to a progressive disturbance in the nutrition of fetal placenta and to maceration and resorption of the fetuses in the uterus without affecting estrus and the faculty of fertilization. The administration of vitamin E in the form of wheat germ oil or suitable concentrates during the earliest stages of pregnancy is capable of anticipating and preventing this fetal destruction. Considerable evidence has been presented in the recent literature as to the efficacy of wheat germ oil in habitual abortion and stillbirth in women.

Last year Evans and his co-workers, O. H. Emerson and G. A. Emerson, succeeded in isolating from cottonseed oil a group of alcohols with the biological activity of vitamin E. These alcohols, the alpha-, beta-, and gamma tocopherols, appear to be isomeres with the empirical formula $C_{29}H_{50}O_2$, in which one of the oxygen atoms is present in a hydroxyl group. Evans and his collaborators have shown that these alcohols have characteristic absorption spectra which resemble that of hydroquinone. Tocopherols are easily oxidized with methyl alcoholic silver nitrate to give colored substances whose ultra-violet spectrum is suggestive of benzoquinone.

Fernholz, one-time student of Windaus in Gottingen, later Merck fellow at Princeton University, who has made important contributions to the chemistry of sterols, bile acids, and sex hormones, and who is now working in the Merck Research Laboratories, has recently studied the action of heat on this group of biologically active alcohols. Fernholz has found that, when alpha-tocopherol is heated, decomposition occurs with the formation of a crystalline compound which was identified as durohydroquinone, a well-known coal-tar product. This thermal degradation seems to be best explained by assigning to alpha-tocopherol the structure of a mono-ester of durohydroquinone. The ultra-violet spectrum of alpha-tocopherol, its insolubility in alkalies, and its high-reducing power as well as the lack of reducing properties in its esters, are in good agreement with such an assumption. Up to now it was generally assumed that vitamin E was chemically related to sterols and sex hormones. This work now establishes that no such relationship exists.

Within the past few years the intense attack on the structure of the vitamins has been eminently successful in leading to methods for their synthesis. The recent elucidation of the structures of vitamins C, B_2, and B_1 (cevitamic acid, riboflavin and thiamine) was followed rapidly by successful syntheses. Vitamin B_1, the anti-neuritic principle, and vitamin C, the antiscorbutic factor, are now being produced by Merck & Co., Inc., for medicinal and industrial use.

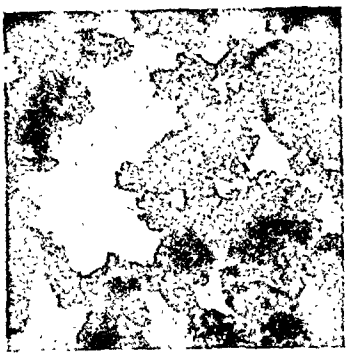
THE AMERICAN COLLEGE OF PHYSICIANS WILL MEET IN NEW YORK CITY, APRIL 4-8, 1938

The Twenty-second Annual Session of the American College of Physicians will be held in New York City, with headquarters at the Waldorf-Astoria Hotel, April 4-8, 1938.

Dr. James H. Means, of Boston, is President of the College, and will have charge of the program of general scientific sessions. Dr. James Alex. Miller, of New York City, has been appointed General Chairman of the Session, and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of Round Table Discussions to be conducted at headquarters.

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(High power view (x120°) of crystalline Bisiodide.)

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Phosphorus	0.620	0.392	0.125	0.093	0.093	0.180
Copper	0.0013	0.0005	0.00017	0.00034	0.000015	0.00023
Vitamin B (B_1)	+ + +	+ +	— to +	+	+ +	+ to + +
Vitamin G	+ + +	+	— to +	+	+ + +	+ + +
Moisture	7.0	8.0	10.9	35.3	87.0	73.7
Protein	15.0	15.2	11.0	9.2	3.3	13.4
Fat	3.0	7.3	1.4	1.3	4.0	10.5
Carbohydrate	70.8	66.2	76.3	53.1	5.0	—
Calories per oz.	106	110	103	74	20	42
Alkaline Reaction	V				V	

Pablum is rich in minerals and vitamins. It is noteworthy that the calcium - phosphorus ratio of Pablum is 1.2:1, similar to that of average whole milk, which is considered the most favorable ratio for retention.

These figures are included to illustrate ordinary nutritional values. Calories, carbohydrates, fats, and proteins no longer constitute a serious nutritional problem.

†PABLUM (Mead's Cereal, thoroughly cooked) contains nine minerals (principally calcium phosphorus, iron, and copper) and vitamins B and G in substantial amounts—in addition to abundance of protein, fat, carbohydrate and calories. Pablum is palatable and requires no further cooking. Supplied in 1 lb. packages.

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Protamine Insulin Compared to Regular Insulin in the Treatment of Diabetes Mellitus*

By

ABEL LEVITT, M.D., F.A.C.P.

and

CHRISTY F. CASTIGLIA, M.D.

BUFFALO, NEW YORK

THIS study is a review of 104 cases of diabetes mellitus in which protamine insulinate has been used since March, 1936. Regular insulin is rapidly absorbed and utilized so that it is almost impossible to produce a comparatively constant level of blood sugar. It was not until Hagedorn and his co-workers introduced protamine insulinate that this fluctuation of blood sugar levels was lessened to conform more closely with the normal. The history of protamine insulinate has been thoroughly reviewed in recent literature and, therefore, needs no further comment. The purpose of this paper is to give a comparative clinical evaluation of regular insulin, plain protamine and protamine zinc.

TYPES OF CASES STUDIED

We have attempted to study this subject not only in cases of uncomplicated diabetes mellitus, but also in cases where diabetic patients have been admitted to the wards of the Buffalo City Hospital for associated conditions. Therefore, we shall present our findings in five groups:

Group I. Those cases of diabetes mellitus where clinically there were no associated conditions.

Group II. Diabetes mellitus accompanied with degenerative changes such as arteriosclerosis, arteriolar-nephrosclerosis, coronary sclerosis, and peripheral vascular disease.

Group III. Diabetes mellitus associated with chronic pulmonary tuberculosis.

Group IV. In acute infections accompanying diabetes mellitus, among which were acute streptococcic infections, diphtheria and furunculosis.

Group V. This group we have designated "miscellaneous" and includes those cases where operative procedures were required.

At the outset of our study, the knowledge of the greater stability of the combined protamine and heavy metal product was not known. Therefore ,our reports will show comparative data obtained with the regular insulin, plain protamine insulin and the protamine zinc insulin.†

DIET

Previous dietetic management of our diabetics consisted of a diet high in carbohydrate, moderate in protein, and low in fat, with the caloric value being approximately 30 calories per kilogram of body weight daily and with an equal division of carbohydrate for the three meals. With the use of protamine zinc insulin we allowed the same caloric value but apportioned our carbohydrate in the ratio of 1/5 for breakfast, 2/5 for lunch, and 2/5 for supper. Hagedorn and his co-workers in their original work gave only about 100 grams of carbohydrate in a ratio of 2/5, 2/5, and 1/5, but we have found that as much as 260 grams, distributed as previously mentioned, does not predicate signs of hypoglycemia.

METHOD OF REPLACEMENT

At the inception, the problem of replacing the regular insulin by the protamine product was speculative. Hagedorn and his co-workers attempted substitutions of protamine insulin before supper with a reduction of the carbohydrate at this meal. Later, many investigators on the other hand, gave the protamine insulin alone in the morning, in sufficient dosage to approximate the previous amount of regular insulin used, or in conjunction with old insulin. Among our replacement methods, we included these plans. In our first use of protamine only those diabetics who had previously used regular insulin were studied. The regular insulin has been replaced by the protamine in the following ways:

1. To one group of patients, plain protamine was given as the evening dose, one hour before the evening meal but supplemented with the regular insulin before breakfast.

2. To a second group, we gave protamine zinc insulin one hour before breakfast, and for the first day or two, supplemented the protamine zinc with a small dose of regular insulin given ½ hour before breakfast, in order to allow for the slow action of the protamine material upon the carbohydrate of that meal.

3. To another group of patients, all severe diabetics, we found it necessary to divide the protamine zinc into two doses, giving one dose one hour before breakfast and the other, one hour before the evening meal.

Before protamine zinc became commercially available, we replaced the protamine standardized patients with regular insulin before they were discharged from the hospital and found this reversion to be well tolerated.

EFFECT ON BLOOD SUGAR

From our study, we have found that the lowest blood sugar level occurs from 18 to 24 hours following the injection of protamine insulin. Thus, if given before breakfast, the lowest blood sugar level will occur during the early morning hours; similarly, if protamine insulin is given with the evening meal, the lowest blood sugar level will occur in the late afternoon. We have used both of the above methods and in

*From the Diabetic Service, Buffalo City Hospital and Department of Medicine, University of Buffalo.

†The protamine zinc insulin was so supplied that each cubic centimeter contained forty units of insulin and approximately 0.08 mg. of zinc in combination with protamine in a precipitated form.

Submitted March 24, 1937.

our opinion the morning injection is preferred, for should hypoglycemia develop as a result of the cumulative effect of the protamine insulin, it could be more readily managed by the patient when at home, than if at work. As with regular insulin, there is a fluctuation of the blood sugar curve throughout the day, and a constant normal level of blood sugar is difficult to maintain with protamine zinc alone. This can be obviated by a supplementary dose of regular insulin. However, this practice necessitates an increased number of injections and tends to nullify one of the most valuable assets of the protamine product.

NUMBER OF INJECTIONS

The slowly soluble protamine insulin is injected into the subcutaneous tissue from which gradual absorption takes place over a considerable period of time. By this method there is a distinct prolongation in the time in which all the injected substance is utilized, resulting in a reservoir of insulin for the diabetic to drain and reducing the daily number of injections. In a reported series of 45 cases by Richardson, Russell & Bowie, it was found that the average number of injections of regular insulin was 2.3 and of protamine insulin 1.4 daily. We have obtained similar results in our series with a reduction from 2.15 injections daily of the regular insulin to 1.45 of the plain protamine and 1.05 injections of the protamine zinc product. In severe diabetics, it was frequently necessary to use as many as four doses daily of the regular insulin, with the fourth injection usually at midnight. Seven of our cases had required such administration with the regular insulin, a feature which was not necessary with the protamine zinc since a single dose was sufficient.

REACTIONS

The blood sugar variations in diabetic individuals which have been difficult to control with regular insulin are frequently maintained closer to normal levels by the use of protamine. The blood sugars reported in our study with protamine are the averages obtained from those taken just before berakfast, lunch, and the evening meal. While the sugar level may frequently go much lower with protamine insulin and may even at times descend to 30 milligrams, the severe symptoms of shock are not as evident. Our findings are consistent with those reported in the literature, that shock is much less frequent with protamine than with regular insulin. Instead of the rapid onset which has been noted in the past with regular insulin, the onset of shock with protamine insulin has been more gradual. This is doubtless due to the gradual lowering of the blood sugar to hypoglycemic levels rather than the rapid fall which occurs with the regular insulin. The most frequent complaint of patients in this series with hypoglycemia was a feeling of uneasiness, weakness and visual disturbance. Diaphoresis in a mild degree usually occurred later in the hypoglycemic state. In several instances sensory disturbances, such as numbness around the mouth and a paresthesia of the fingers and toes was noted. In some cases headache preceded the shock by hours, while in others it followed the treatment for hypoglycemia. Hypoglycemia due to protamine insulin, when it does occur, necessitates prolonged and frequent treatment in order to combat the prolonged effect and continuous supply of the protamine zinc insulin.

The following tables include our results with the groups as previously indicated:

TABLE I

Uncomplicated diabetes

	Cases	Av. Daily Units	Av. Daily Inj.	Av. Bld. Sugars
Reg. Insulin	48	47.45	2.46	205
*Plain Prot. Plus Supplementary Reg. Insulin	20	47.45	2.46	205
Reg. Insulin Before use of *Plain* Protamine	9	53.4	2.66	195.4
Plain Protamine Used Alone		51	2.1	153
Reg. Insulin before use of Protamine Zinc	22	47.3	2.5	193.3
Protamine Zinc Used Alone		35	1.16	150.6

*Three of the cases of this group of 20 were later treated with protamine zinc alone. All plain Protamine insulin given one hour before supper, and supplementary regular insulin given one-half hour before breakfast.

In a study of the comparative value of the regular insulin used in conjunction with plain protamine or with the protamine zinc compound in 48 cases of uncomplicated diabetes mellitus, it can be seen that the average daily number of units of regular insulin used was 47.45, while the average number of injections was 2.46 and the average blood sugar 205 mg. When plain protamine was supplemented with regular insulin in 20 cases out of the above 48, there was no change in the number of units, injections or blood sugar level. Nine cases of this group which required an average of 53.4 units of regular insulin daily, were reduced to 51 units of plain protamine while the average number of injections of 2.66 in these cases was reduced to 2.1 and the blood sugar level which had previously been 194 mg. was reduced to 153 mg. So that plain protamine insulin when used alone seemed beneficial in every way. 22 patients of this group who required an average of 47.3 units of the regular insulin, required only 35 units of the protamine zinc. The average number of daily injections dropped from 2.5 to 1.6 and the average blood sugars from 193.3 mg. to 150.6 mg. It can, therefore, be seen that in this group of 48 cases of uncomplicated diabetes mellitus with plain protamine alone there was a reduction in the number of daily units required, the number of daily injections and also a lower level of blood sugar prevailed. This was still further improved with the use of the protamine zinc product (Table II). In this group there were 19 cases of diabetes mellitus complicated by the cardiovascular-renal sclerotic syndrome. When placed on regular insulin with a maintenance diet these patients were sugar free with average daily units of 33.3 of regular insulin and required an average of 2.15 injections daily. This kept the blood sugar at an average of 178.4 mg. Twelve of these cases were then placed on plain protamine supplemented with the regular insulin and in order to keep them sugar free, they required an average of 43.4 units daily, while the average number of injections was reduced to 2 and

the blood sugar ranged about 161.2 mg. It is thus evident that the plain protamine in conjunction with the regular insulin results in an increase in the total amount of insulin used, but reduces the average number of daily injections and blood sugar levels. Six

TABLE II

Diabetes mellitus with degenerative diseases

	Cases	Av. Daily Units	Av. Daily Inj.	Av. Bld. Sugars
Reg. Insulin	19	33.3	2.15	178.4
Plain Protamine Plus Supplementary Reg. Insulin	12	43.4	2	161.2
Reg. Insulin Before use of Plain Prot.	6	34.5	1.93	161
Plain Prot. Alone		33	1.6	163
Reg. Insulin Before use of Protamine Zinc	3	37	2.5	208
Protamine Zinc Alone		12	1	162.2

patients of this group under regular insulin required an average of 34.5 daily units, with an average of 1.93 daily injections and showed average blood sugars of 161, and when placed on plain protamine alone showed a reduction of units to 33, reduction of injections to 1.6, while the blood sugars remained at 163 mg. Three cases of this group were then placed on protamine zinc alone and as seen from the (Table II) there was a marked reduction in the total amount of insulin required, the average daily number of injections and the height of the blood sugar.

TABLE III

Diabetes mellitus associated with chronic pulmonary tuberculosis

	Cases	Av. Daily Units	Av. Daily Inj.	Av. Bld. Sugars
Reg. Insulin	12	57	1.9	154
Plain Prot. Plus Supplementary Reg. Insulin	11	54	1.9	158
Reg. Insulin Before use of Plain Prot.	2	21	1.15	146.5
Plain Prot. Used Alone		19	1.5	171

Twelve cases of active pulmonary tuberculosis associated with diabetes required on an average of 57 units of regular insulin daily with an average of 1.9 injections. Their blood sugar hovered around 154 mg. Eleven of this group were then placed on plain protamine supplemented with regular insulin and the average daily units were reduced to 54, the number of injections remained the same but the blood sugar increased slightly to 158 mg. In this group due to the presence of the pulmonary activity and the general mental attitude of the patient, it was extremely difficult to obtain full cooperation in maintaining dietary requirements, so that there was considerable fluctuation in the results. Two patients of this group required an average of 21 units of the regular insulin daily and 1.15 daily injections, which resulted in an average blood sugar of 146.5 mg., but when placed on plain protamine the average daily units were reduced to 19, while the number of injections increased to 1.5 and the blood sugar increased to 171 mg. This, however, is too small a series from which to draw any conclusions.

Only one case has been given protamine zinc insulin and this is reported as a special case study and not included in Table III.

TABLE IV

Diabetes mellitus complicated by acute infections

	Cases	Av. Daily Units	Av. Daily Inj.	Av. Bld. Sugars
Reg. Insulin	12	37.2	2.3	194.6
Plain Prot. Plus Supplementary Reg. Insulin	9	38	1.4	147
Reg. Insulin Before use of Plain Prot.	3	26.5	2	211
Plain Prot. Used Alone		16	1	130
Reg. Insulin Before use of Protamine Zinc	4	46.9	2.84	274.9
Protamine Zinc Used Alone		32.9	1	133.9

A group of 12 diabetics previously controlled with the average daily units of 37.2 of regular insulin and requiring 2.3 injections and showing an average blood sugar of 194.6 were admitted to the hospital at different times with acute infections. Nine of this group were placed on plain protamine supplemented by regular insulin and required 38 units on an average daily, 1.4 injections and their average blood sugar was reduced to 147 mg. These, therefore, required a slight increase in the amount of insulin, but the injections and sugar levels were reduced. Another group of 3 patients who had required an average of 26.5 units daily of regular insulin with 2 injections and had an average blood sugar of 211 mg. were then placed on plain protamine alone and this resulted in a reduction of the average units to 16, the number of injections to 1 and the blood sugar to 130. Four patients of this group were then placed on protamine zinc alone. These four, while on regular insulin required on an average of 46.9 units daily with 2.8 injections and showed a blood sugar of 274.9. When changed over to protamine zinc the average daily number of units became subsequently reduced to 32.9, the number of injections to 1 and the blood sugar to 133.9 mg.

This group tends to show that with plain protamine supplemented by regular insulin the total number of units is increased but the average number of injections and blood sugar is reduced. Furthermore plain protamine alone results in a general reduction, while even better results are obtained with protamine zinc.

...Three diabetics who were admitted to the hospital

for some surgical procedure, following the operation were placed on their previous maintenance diet. It can be seen from the data above that with plain protamine, the total number of units and the number of

TABLE V

Diabetes mellitus — Miscellaneous cases

	Cases	Av. Daily Units	Av. Daily Inj.	Av. Bld. Sugars
Reg. Insulin	3	23	1.8	123
Plain Prot. Plus Supplementary Reg. Insulin	1	37	2	161
Reg. Insulin Before use of Plain Prot.	2	16	1.7	100
Plain Prot. Used Alone		14	1	135

injections were reduced without much change in blood sugar.

We have reviewed 104 cases of diabetes under treatment with protamine insulinate. The average daily number of units of regular insulin required by the entire group was 39.59, while the average daily injections were 2.15. This brought about an average blood sugar of 171 mg. Fifty-three cases of this group were placed on plain protamine supplemented with regular insulin and the average daily units were 43.97, the average daily injections were reduced to 1.95.

TABLE VI

Summary

	Cases	Av. Daily Units	Av. Daily Inj.	Av. Bld. Sugars
Reg. Insulin	104	39.59	2.15	171
Plain Prot. Plus Supplementary Reg. Insulin	53	43.97	1.95	162.4
Reg. Insulin Before use of Plain Prot.	22	30.24	1.88	162.78
Plain Prot. Used Alone		26.6	1.45	150.4
Regular Before Use of Protamine Zinc	29	43.7	2.61	228.9
Prot. Zinc Used Alone		26.6	1.05	148.9

This corresponds to our findings in the individual groups, where the total insulin was increased, but the average number of injections and blood sugar levels were decreased. In 22 cases, where plain protamine was used alone, the average daily units were reduced from 30.24 to 26.6 and the number of injections from 1.88 to 1.45. With the protamine zinc alone in 29 cases the average number of units of regular insulin was reduced from 43.7 to 26.6 and the number of injections from 2.61 to 1.05.

One difficulty we have noted is that we were unable to determine how much of a cumulative action we would obtain from protamine zinc. As we are now discharging patients standardized on protamine zinc on the wards to our outpatient clinic, we not infrequently have some return with reports of hypoglycemia. It is, therefore, essential that these cases be constantly observed for a considerable period afterwards in order to determine the amount of protamine zinc they require in carrying out their usual activities.

More recently we have had an opportunity to use U-80 protamine zinc insulin. This preparation seems more efficient in controlling the blood sugar level than the U-40 material reported above. In comparing the U-40 and U-80, in a group of five patients who required 67.4 average daily units of the former, this was reduced to 60.8 of the U-80 and the blood sugar levels reduced from 103.6 to 100.9. It has an added advantage to patients who require large doses of insulin.

CONCLUSIONS

1. Our studies tend to show that protamine when supplemented with regular insulin results in an increase in the total number of units per day but there is a slight reduction in the number of injections, and most important a lower and more normal blood sugar level.

2. When plain protamine is used alone there is a considerable reduction both in the amount of insulin and in the number of injections, while the blood sugar level is not only reduced but frequently is considerably below the normal level approximately 24 hours after the injections.

3. Protamine zinc gives the best results in all of the above mentioned points.

CASE REPORTS

Case I. L. M., a colored female, 43 years of age, was admitted to the diabetic service of the Buffalo City Hospital with a history of diabetes of six months duration. No family history of this disease.

Physical examination revealed a moderately obese colored female not acutely ill, no physical abnormalities were noted. The diagnosis was diabetes mellitus and moderate obesity. The patient weighed 161 pounds and was placed on a diet of 160 grams of carbohydrate, 70 grams of protein and 80 grams of fat. Her blood sugar upon admission was 362 mg. per 100 c.c. of blood and there was 9.2 grams of urinary sugar present. At this time she was given regular insulin, 10 units in the morning and 8 units at night. This insulin was increased to 12 units in the morning and 12 units in the evening and blood sugar at that time was 198 mg. while there was still glycosuria. Protamine zinc was started and the patient received 20 units one hour before breakfast, which was gradually decreased to 10 units in one injection one hour before breakfast. The blood sugars varied from 90 to 138 mg. throughout the day and there was no glycosuria. This patient is a mild diabetic and was standardized within ten days and has remained with same dose of protamine since discharged from the hospital.

Case II. B. L., a white female, 59 years old, was admitted to the diabetic service with a history of diabetes for the past five years. She had had polydypsia, polyuria, weakness, pruritus and a loss of 40 pounds of weight over this period of time. Physical examination was essentially negative. Her weight was 127 pounds and she was placed on a diet of 220 grams of carbohydrate, 70 grams of protein and 70 grams of fat. Her blood sugar on admission was 246 mg. and urinary sugar 7.5 grams. Regular insulin 18 units before breakfast and 15 units before supper was given which was increased to 35 and 25 respectively and at this time her blood sugar was 262 mg. and the urinary sugar was 4 grams. Since the blood sugar remained persistently high and glycosuria continued, this patient was

placed upon 55 units of protamine zinc one hour before breakfast followed by 14 units of regular insulin one-half hour before breakfast and 10 units of regular insulin one-half hour before supper. The protamine zinc insulin was gradually decreased to 35 units in one daily injection given one hour before breakfast. Her blood sugar values with only one injection varied from 92 to 118 mg. throughout the day and her urine remained sugar free.

Case III. M. H., a white female, age 19, was admitted to the acute communicable service with a history of an upper respiratory tract infection of one month duration with nasal discharge and sore throat one week prior to admission. She had had diabetes for the past 5 years. Physical examination revealed a well developed white female acutely ill with a temperature of 101.4, pulse 120 and respiration of 36. Her pharynx and larynx were inflammed and the tonsils cryptic, pus was present in both nares and the turbinates enlarged. The chest was clear and resonant and the heart was regular but rapid.

There was no skin eruption and the remainder of the examination was essentially negative. Positive nose and throat cultures for diphtheria were obtained and these proved to be virulent by the guinea pig test. The diagnosis was (1) acute laryngitis and pharyngitis and (2) diphtheria carrier.

The patient weighed 142 pounds and was given a diet of 160 grams of carbohydrate, 70 grams of protein and 80 grams of fat. Her blood sugar at time of admission was 562 mg. and there was 34.5 grams of urinary sugar. Regular insulin therapy was instituted in a dosage of 35 units in the morning and 24 units before supper and 10 units at midnight which was gradually increased to 70 units before breakfast, 15 before lunch, 40 before supper and 10 at midnight, during which time blood sugar never fell below 400 mg. and there was persistent glycosuria. Protamine zinc insulin was started in dosage of 65 units in the morning and 25 units at night. Eventually the night dose was discontinued and the patient was given only a single injection of 80 units one hour before breakfast. Following the use of the protamine zinc the blood sugars approached normal and in no instance following the use of this product did it go above 153 mg., while the urine remained sugar free. At present the patient is up and about, the temperature, pulse, and respirations are within normal limits, but nose and throat cultures remain positive for virulent diphtheria organisms.

Case IV. R. W. is a white male, age 13, who was admitted to the tuberculosis service with a history of diabetes of 2 years duration. His father died of chronic pulmonary tuberculosis and diabetes mellitus. Physical examination revealed an acutely ill and emaciated white male. Positive findings on examination were bilateral apical infiltration with cavitation. His heart was rapid but regular and the other systems were essentially negative. His weight at this time was 53 pounds while his temperature was 103, pulse 130 and respiration 26. He was diagnosed as (1) Chronic pulmonary tuberculosis, (2) diabetes mellitus, (3) malnutrition and (4) anemia. All sputa were positive for tubercle bacilli and X-ray showed bilateral apical infiltration with multiple cavitation. He was given a diet of 230 grams of carbohydrate, 80 grams of protein and 110 grams of fat, and placed on regular insulin 30 units before breakfast, 10 before lunch, 30 before supper and 5 at midnight. His blood sugar at this time was 440 mg. and there was 62 grams of urinary sugar. Because the blood sugar remained persistently high the regular insulin was increased to 60—30—30—10 and at this time the blood sugar was 210 mg. and glycosuria persisted. Therefore, it seemed advisable to inaugurate protamine insulin therapy and he was given at the beginning 75 units of protamine zinc one hour before breakfast and 25 units before supper. Within four weeks the evening dose was discontinued and the patient controlled upon 85 units of protamine zinc insulin one hour before breakfast. The blood sugar levels were lowered to within normal limits and the urine remained sugar free. At the present time the patient weighs 79 pounds and the most recent X-ray shows a tendency toward fibrotic healing in both apices.

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The Effect of Nicotine on Intestinal Peristalsis

By

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YEARS ago I began using nicotine in an attempt to learn more about the structure and function of the intestinal plexuses. I could, of course, read in any textbook the statement that nicotine blocks the peristaltic waves while it leaves unchanged the rhythmic contractions, and that it blocks the effects of stimulating the vagal and the preganglionic sympathetic neurones while it does not block the effects of stimulating postganglionic sympathetic fibers. But I knew that in recent years a number of these old accepted statements had come to be questioned, I knew that the whole conception of synapses and the effects of drugs on them was changing, and besides, there were a number of interesting questions that might yet be answered by further study of the action of nicotine on the bowel. I wanted to see how its action on the neurones of the gut would compare with that of

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anoxemia. Using rabbits as test animals and anoxemia as an injurious agent, I had found that some mechanism, probably a nervous one, interrupted by synapses, and very helpful in the production of peristaltic rushes, became disrupted from ten to thirty minutes after the stoppage of the circulation. What appeared to be nervous conduction along short conducting paths was lost in about two hours, while nervous conduction through long unbroken pathways, and the rhythmic contractions of the muscle began to fade out only after seven hours or more. In all these experiments the tissue was kept at 38° C. in aërated Locke's solution.

I here report the results of using nicotine much as I used anoxemia to obtain information as to the structure of the enteric nervous system (3). Before describing the experiments, it will be helpful to stop for a moment to see what one can hope to accomplish with nicotine. Years ago, when I began to work with it, I assumed, as do most writers of articles and textbooks, that it would block transmission through sympathetic ganglions and across such synapses as are believed to exist between the vagal nerve endings and the neurones in the plexuses of the heart and intestine; but the more I read, the less certain I became that nicotine could be counted on always to do the things that have been expected of it. Thus, years ago, Langley (49) and others noticed that it commonly did not interrupt the transmission of reflexes through centers in the medulla and spinal cord, and that sometimes it did not have the expected effects even on the nerve centers in the bowel (Langley and Anderson).

Recent studies have shown also that the drug can affect nerve endings, and that the disturbances of respiration are not due to the disruption of synapses in the center in the medulla but to a curare-like effect on phrenic nerve endings in the diaphragm (Dixon, Langley and Dickinson, Thomas and Franke, Franke and Thomas, Gold and Brown, and Ing). Still more disturbing was the discovery that in large doses it actually improves the transmission of stimuli from the vagal neurones to those of the myenteric plexus (Langley and Anderson, Thomas and Kuntz (74), Mulinos, Henderson). To be remembered also is the fact that, in very large doses, it can block transmission through nerve fibers (Pi-Suner and Raventos, and Raventos (67, 68)) and it can injure muscle (Lapicque) and other tissues (Greenwood).

Often a dose which will interrupt synapses in one ganglion or set of ganglions, as in the heart, will leave others, as in the intestine, unaffected; or with a certain dosage, the effects of vagal stimulation on the heart will be blocked while transmission of stimuli from one vagus to the other through the center in the medulla can still be effected (Pi-Suner and Raventos). Furthermore repeated doses commonly fail to produce the effect of the first dose (Gold and Brown).

Writers on the subject commonly assume that nicotine paralyzes ganglion cells, but Langley (49) could not be sure of this, and I have been unable to find much evidence of it in the literature. For that matter, I cannot find much on how one would tell when a ganglion cell has lost its function. Perhaps the best evidence that nicotine can injure a ganglion cell was obtained recently by Heinbecker and Bishop while studying the heart of Limulus. In this organ, as is well known, the beat of a muscle, itself capable of rhythmic activity (Carlson and Meek, Garrey, Crozier and Stier, Heinbecker and Bishop), is normally influenced by outside ganglion cells (Heinbecker). Here nicotine promptly blocked the usual effects of stimulating the extrinsic inhibiting and accelerating nerves; after from fifteen to thirty minutes, the electrical record of discharges coming from the ganglion cells faded out, and from five to fifteen minutes after this the heart ceased beating, although the muscle was still responsive to electric stimulation of the median nerve-cord.

These observations indicate that the synapses between the extrinsic nerves and the local ganglion cells are most sensitive to attack by nicotine; next in susceptibility probably come the ganglion cells, next the function of rhythmicity in the muscle, and last of all the functions of conduction in local nerve fibers and their endings, and of irritability in the muscle. Instructive also in this regard is the old experiment of Carlson (1909) who found that a 1:1000 solution of nicotine applied to the heart of Limulus took ninety-four minutes to stop rhythmic activity in the ganglion, 265 minutes to destroy irritability and conductivity in the nerve plexus, and 1140 minutes to destroy irritability and contractility in the muscle.

That in the heart of Limulus the pace-making impulses come only from the large unipolar ganglion cells found in certain parts of the nerve cord and not from the small multipolar cells or from the axone fibers is now strongly indicated by the work of Heinbecker. The evidence presented in the two papers by Heinbecker and Heinbecker and Bishop suggests, then, that nicotine puts a stop to the rhythmic impulses which arise in the big pace-making ganglion cells.

In the case of the bowel of mammals the assumed synapse at the end of the vagal fibers is sensitive to small doses and extremely resistant to large doses of nicotine (Kuntz and others (47)); the synapses in Auerbach's plexus seem to be highly susceptible, as shown by the usual prompt stoppage of rush waves; and the ganglion cells, much perhaps as in the heart of Limulus, are apparently fairly susceptible, granting that one can assume this from the fact that nicotine suppresses the rhythmic action currents of the gut while it leaves the muscle beating regularly at a slower rate (Berkson, Puestow (7, 8, 9, 10, 11)). It is conceivable, of course, that in the bowel the suppression of the rhythmic currents is due to injury to synapses in an oscillating nervous circuit such as that conceived by Lorente de Nó.

According to Himwich and Fazikas, nicotine probably interferes with the metabolism of nervous tissue by blocking the dehydrogenation of lactic and succinic acids. According to Ing, nicotine, like curarine, is a chemical antagonist to acetylcholine, which may account for its ability to block conduction in some synapses. Curiously, physostigmine is able to restore the function of vagal synapses in the heart after they have been blocked by nicotine or barbiturates (Linegar, Dille and Koppanyi).

Efforts have been made to throw light on the point of attack of nicotine by comparing its actions on normal bowel and on bowel from which Auerbach's plexus has been stripped with the help of a dissecting needle. Thus, Magnus concluded that "plexus-free" strips of intestinal muscle would not respond to nicotine, but van Esveld and Gasser observed depression with large doses; it was only the stimulating effect that could not be obtained.

Unfortunately, definitely plexus-free muscle can probably never be secured by dissection. One can get muscle free from either Auerbach's or Meissner's plexus, but one cannot remove the fine intramuscular plexus of fibrils which some observers say are related to connective tissue and others feel sure are nervous in origin (van Esveld, Tiegs (76, 77), Schabadasch). As Bayliss once said, however, it does not seem probable that such fibers or the occasional ganglion cells that can be found on blood vessels can serve to originate the regular rhythmic contractions of the muscle. The recent observations of Heinbecker, already quoted, make this assumption still more doubtful, but still it cannot be dismissed.

So far as the action of nicotine on the bowel is concerned, the classic experiment is the one in which the drug was shown to block the effect of stimulating the preganglionic but not the postganglionic fibers (Langley and Anderson, Langley (48), Bunch). From this it was assumed that the preganglionic fibers which enter the bowel are connected by synapses to neurones in Auerbach's plexus, while the postganglionic fibers run directly to the muscle. Much confirmation of this idea has been published by Nolf and others, but in recent years a number of observers besides myself have found that large doses of nicotine can block the effect of stimulating the postganglionic fibers (Thomas and Kuntz (47, 75), Hendricks and Thienes).

In the face of the many contradictions to be found in the literature on nicotine, and the many puzzling observations which will be recorded in this paper, it would seem unwise to theorize much about the results of experiments done with this drug. This is particularly true at a time when our conceptions of function at nerve endings is changing rapidly, and the actual chemical intermediaries between nerve and muscle are becoming known.

TECHNIC

The technic used in the studies here reported has been described elsewhere (1). Briefly, rabbits were anesthetized with urethane, the spinal cord was pithed distal to the fourth thoracic segment, and the abdomen was opened under a bath of warm Locke's solution. Records were obtained with the help of apparatus described elsewhere (2).

There were two main ways open for studying the effects of nicotine on the gut. The first method, in which the drug was injected intravenously or intramuscularly, had the disadvantage that it usually put a stop to the peristaltic rushes which I wished to study. The second method consisted of connecting a segment of gut to light recording levers, bathing it for a few minutes in a solution of the drug, dropping it back into the tank, and then studying the behavior of rushes that reached or passed through it.

As was to be expected, the concentration of nicotine necessary to injure synapses in the bowel had a decided effect on some of the functions of the brain. Thus, in a medium-sized rabbit, 0.05 c.c. of a 1 per cent solution, or 0.5 mg., injected into the ear vein usually produced some change in the rate and depth of the respiratory movements; occasionally it produced convulsions, and sometimes if the animals were not helped to breathe, it promptly killed. Usually the peristaltic rushes were stopped. With twice the dose, or 0.1 c.c., peristaltic rushes usually stopped and the animal died unless respiration was maintained artificially.

When the drug was injected intramuscularly, at least 0.02 c.c. of the undiluted substance was needed to get results. When an animal survived such a dose it was often possible, a few minutes later, to give larger doses, and sometimes, with respiration maintained artificially, the animal would live on after huge doses of the poison had been given.

Dosage of nicotine used. Because varying dosage can greatly modify the effects obtained, it might be well to review briefly the concentrations of the drug used by a number of investigators. To abolish the effects of vagal stimulation on the bowel Bayliss and Starling used 0.3 c.c. of a 1 per cent solution. Mulinos used from 1 to 10 mg. per kilogram of body weight. Raventos (69) blocked conduction in the vagus nerve with a solution of 0.5 to 1 per cent. Thomas and Kuntz used from 1 to 20 mg. per kilogram to paralyze vagus endings and from 25 to 50 mg. to restore them to activity. From 2000 to 3000 mg. per kilogram were then required to stop them again. Mulinos restored the vagus effect with from 20 to 60 mg. To "denervate" the excised bowel Thomas and Kuntz used a 0.2 per cent solution. Rhythmic contractions were abolished with the help of a 0.5 per cent solution. Heinbecker and Bishop used a 0.5 per cent solution on the heart of Limulus.

Hendricks and Thienes abolished the effects of stimulating postganglionic sympathetic fibers with a 1:1000 solution. Nolf used from 1:10,000 to 1:1,000,000 on the bowel of the chicken, the latter strength being apparently sufficient for the blocking of synapses. Bunch used 1 mg. per kilogram to abolish the effects on the intestine of stimulating the extrinsic nerves. Langley (49) usually used a 1 per cent solution. Bayliss and Starling stopped the rhythmic contractions of the bowel by injecting 2 or 3 c.c. of a 1 per cent solution into a fairly large dog. They blocked vagus nerve endings with 0.3 c.c. of a 1 per cent solution. Franke and Thomas (28) lost several dogs after giving doses of from 2 to 4 mg. per kilogram. Macht paralyzed the ureter with a 1 per cent solution. My impression is that if one hopes to study the effect of the drug on synapses or ganglion cells one should use the smallest dose that will stop function in these structures; with larger doses the drug is likely to act as a general protoplasmic poison.

Effects of altered nicotine. From the start of my work I had difficulty in obtaining the results I had been led to expect with nicotine, but as months passed I ran into an even worse trouble, namely, I could not duplicate the results of experiments performed earlier in the year. The nicotine I was using looked and smelled all right, and when injected into animals caused death in the usual way; there was the usual beady appearance of the gut, and the usual slowing and strengthening of the rhythmic contractions, but no longer could I be sure that even a large dose given by vein would stop the peristaltic rushes. Curiously, the drug still interfered with the rushes when, well diluted, it was applied directly to segments of gut. In one animal, killed by repeated injections of a large dose, a fairly normal rush was seen just before death, and shortly after, two good rushes were elicited by an intravenous injection of epinephrine.

Finally, it occurred to me that I was using nicotine from a bottle which had been around the laboratory for some time. Although this bottle was made of dark amber glass I still feared that light might have af-

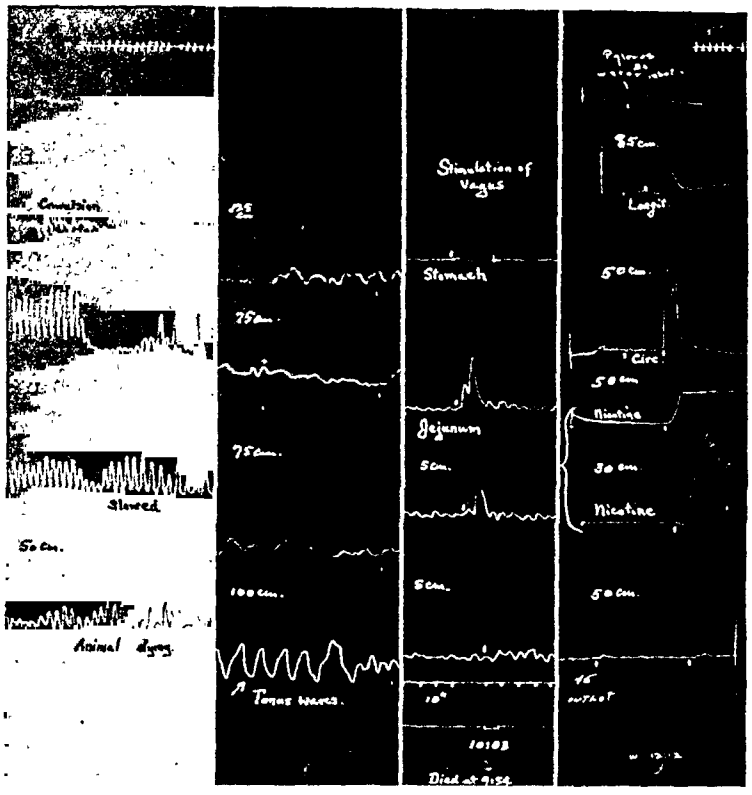


Fig. 1*a*. Inhibition of rhythmic movements and slowing of the rate of rhythmic contraction in an animal dying of nicotine poisoning; *b*, tonus waves in an animal severely poisoned with nicotine; *c*, responses to stimulation of a vagus nerve in an animal that had died nine minutes before from an overdose of nicotine, and *d*, defective emptying in a segment poisoned with nicotine.

fected the contents. Accordingly I opened a new bottle, and immediately found that its contents would almost always stop peristaltic rushes. It may be of interest in this connection that Pacini and McGuigan and Wakeham and Tracy found marked changes in the toxicity of nicotine exposed to ultraviolet radiation.

My experiments revealed, then, a curious change in nicotine which left it as toxic as ever to the central nervous system but without some of its usual paralyzing effect on the mechanism that produces peristaltic rush. It would be helpful if someone could penetrate the secret here concealed. Certain it is that hereafter any physiologist who wishes to study the effects of nicotine on the bowel must first make sure that his supply of the drug is fresh and capable of stopping peristaltic rushes.

EFFECTS OF NICOTINE HERE REPORTED

Appearance of the nicotinized bowel. The nicotinized bowel commonly took on a beaded appearance which suggested either an incoördination of the activity of the muscle bundles or a peculiar form of local stimulation. The appearance of this beadiness was helpful in that it served to show the experimenter when enough nicotine had been given to produce an effect. It probably was not due to failure of conduction along nerve fibers because sometimes it disappeared after a few minutes, at a time when the nervous mechanism that facilitates the passage of rushes was still out of order. Furthermore, such beadiness is not typical of bowel which has lost its power to conduct through long continued anoxemia. I think, therefore, that the beadiness is due at least in part to the well-known stimulating effect of nicotine on nervous tissue. On one occasion a slow rush was seen to pass through a beady bowel, which suggested that if rushes are dependent on the integrity of synapses, then beadiness cannot be depended on as a sign of injury to these structures.

Effect on rhythmic contractions. I found, as others have done, that the rhythmic contractions are usually slowed, are often made more regular, and the amplitude is commonly increased (Fig. 1, *a*). The greater amplitude shows that there is no impairment of conduction in the fibrils which presumably enable many muscle fibers to contract as a unit. As Bayliss and Starling and Trendelenburg noted years ago, the fact that the rhythmic activity is improved at a time when the peristaltic rushes are stopped, and the animal is perhaps dying, indicates that nerve cells are not important in producing the phenomenon. Their argument is even stronger now that Heinbecker and Heinbecker and Bishop have presented evidence indicating that nicotine does put a stop to the activity of pacemaking ganglion cells.

A slowing of the rhythmic contractions similar to that observed with nicotine is seen immediately after the death of the animal or after the removal of the

bowel to a tank of oxygenated Locke's solution, or after degenerative section of the vagus or the splanchnic nerves. This suggests that although the muscle alone is capable of rhythmic contraction, the rate at which this contraction is maintained is normally elevated by some stimulus or chemical substance which arrives by way of the extrinsic nerves of the bowel.

The situation may be similar to that in the heart of Limulus where nerve impulses alter the rhythmic activity of the muscle without imposing their rhythm on it (Heinbecker and Bishop). As Hoagland pointed out, rhythms can be altered by chemical substances that simply change the rate of the metabolic processes in the nerve cells.

van Esveld concluded from his work that the rate of rhythmic contractions in "plexus-free" intestinal muscle is not affected by nerve poisons, but Figure 3 in Gasser's article would indicate that it can be slowed by nicotine. Thomas and Kuntz (75) concluded that when nicotine slows the rate of rhythmic contractions it is a sign that the drug has thoroughly denervated the bowel.

Curiously, Elliott found that although nicotine did not stop the rhythmic movements of the cat's bladder, denervation produced by picking off the ganglion cells with the help of fine forceps and a dissecting microscope, did stop them.

When, as sometimes happens with massive doses, the rhythmic movements of the bowel are stopped by nicotine, the effect is probably a toxic one on the muscle. Puzzles remain, however. Thus, in one of my experiments, an initial dose of 0.05 c.c. of nicotine given intramuscularly almost killed the animal and almost stopped the rhythmic contractions. Later, when after a dose of 0.45 c.c., respiration was almost stopped and death was imminent, the rhythmic activity of the bowel returned to normal.

Strangely, in a number of the animals killed by nicotine, the rhythmic activity of the bowel was good up to the moment of death, and then the contractions stopped just as they commonly do when a normal rabbit dies (Fig. 1, *a*). Such stoppage in normal animals is not due to anoxemia alone, because when the bowel is cut away from the mesentery, contractions return, and they can then be maintained for hours. There are reasons for believing that the pause is due to chemicals formed in the blood at the time of death.

Effect on short nervous tracts in the bowel. In rabbits the contraction produced by an interrupted electric stimulus spreads out for from 5 to 20 cm. along the bowel. This type of conduction, which seems to be mediated by nerves (Alvarez and Hosoi, Elliott, Eugling, Henderson) was interfered with by nicotine only when the dose of the drug was so large as probably to injure the muscle and to destroy its ability to contract. From this and other experiments to be described later, I conclude that nicotine, in doses sufficient to stop peristaltic rush, leaves the intestinal nerve fibers and nerve endings in good working order. About the only evidence against this view is that of Fleisch who thought that the short-distance conduction observed in the guinea-pig's bowel was blocked by nicotine. He may perhaps have used a dose that injured the muscle.

Effects on stomach and colon. It is interesting to note here that Cannon (15) found that the giving of nicotine or the making of several parallel cuts through the muscular coats of the stomach was without effect on the gastric waves (see also Thomas and Kuntz (75)). Similarly, nicotine had no effect on colonic reverse paristalsis (Elliott and Barclay-Smith, Cannon (15, 16)). These facts fit in with others, all of which indicate that the conducting mechanisms in the stomach and colon are different from those in the small intestine.

Effects on tonus waves. The tonus waves of the bowel were sometimes abolished by nicotine, at least for a time, which perhaps fits with the conviction of Gross and Clark that these waves are neurogenic in origin. Kuntz and Thomas (47) also noticed a loss of tonus waves after giving nicotine. I found them, however, well marked in records made from heavily nicotinized bowel, so the subject is still open to debate (Fig. 1, *b*).

Effect on irritability. The irritability of the bowel to faradic stimulation was not lowered until large doses of nicotine were used, and even then it was not always affected adversely. I have obtained excellent responses to faradic stimulation in bowel just removed from animals killed by an overdose of nicotine.

Effect on the vagal synapse. I confirmed the statements of Thomas and Kuntz, Mulinos, and Henderson to the effect that nicotine in large doses does not block the effect on the bowel of vagal stimulation. Actually, I obtained records showing definite response to such stimulation in the intestine of animals which, a few minutes before, had succumbed to a large dose of nicotine (Fig. 1, *c*). In one animal these responses continued for twenty minutes after death, or until the moment when one would expect anoxemia alone to put an end to function in the synapse.

I assume that such a synapse exists partly because it has been seen by histologists (Hill, Irwin). Another argument in favor of its existence is the old one of Langley (50) who pointed out that there are not enough nerve fibers in the vagus bundles to connect with the millions of muscle cells in the bowel. He thought there must be intermediary nerves in Auerbach's plexus, but now that we have the new humoral explanation of nerve action, and now that Bunting, Meek and Maaske, Finkleman, and Dale and Feldberg have demonstrated what looks like a chemical transmission of nervous effects to the smooth muscle of the intestine, Langley's reasoning is not so impressive. Formerly I might have argued in favor of the synapse idea from Klee's and my observations that the latent period of stimulation through the vagus is much longer than that after direct stimulation of the bowel, and that the bowel suddenly fails to respond to stimulation of the vagus nerves after the circulation has been shut off for approximately twenty minutes, but now it is possible to explain such things on the basis of the new ideas of acetylcholine formation.

If one assumes the presence of a "synapse" at the end of the vagal fiber, one must conclude that nicotine interferes with its function in small doses but not in large. Thomas and Kuntz concluded that the blocking effect of small doses is probably due to some form of inhibition. At first glance one would expect a vagal synapse in the bowel to be blocked by atropine, but Bayliss and Starling could not obtain any blocking either with this drug or with curare.

Effect on peristaltic rush. Bayliss and Starling early reported that nicotine stops traveling waves and

disrupts the myenteric reflex, and later these observations were confirmed by Langley and Magnus, Cannon and Trendelenburg.

When I began my work I, too, found that a dose of nicotine sufficient to alter respiration and to modify the appearance of the bowel usually put a stop to peristaltic rushes so that they could no longer be elicited in the usual way by squirting fluid into the duodenum. Often there would be one or two rushes during the stage of apparent stimulation due to the arrival of the drug in the tissues, and then there would be no more. There were, however, puzzling exceptions to the rule, and sometimes the rushes did not stop until several doses had been given.

Obviously, just one *normal* rush seen in an animal dying from an overdose of nicotine freshly obtained from a reliable drug house should be enough to upset all deductions drawn from many experiments in which rushes could not be obtained. The difficulty comes in telling whether or not the rushes seen in nicotinized animals are normal. It would seem as if a careful study of the graphic records should have settled this point, but it did not always do so for reasons that I have given elsewhere and which I will repeat further along in this paper.

Another difficulty seems to arise from the fact that many of the rabbits one buys are full of parasites and perhaps sickly. At any rate, the bowel in many of the animals seems to be so sluggish and unresponsive that any little extra handicap puts a stop to all peristalsis. After working with such animals for a while one may think that certain results have been obtained often enough to settle a point, and then along comes an animal, perhaps unusually healthy and vigorous but at any rate with rushes so powerful that they keep running in spite of severe poisoning by nicotine or anoxemia, and then the investigator does not know what to conclude.

In several experiments in which the effect of a moderate dose of nicotine wore off in half an hour or so, normal rushes reappeared, showing that the injury done was not irreversible. Prompt recovery was the rule when segments of bowel were soaked in a solution of nicotine.

Sometimes, for a minute or two following the injection of nicotine, widespread intestinal contractions were seen which suggested the passage of a rush, but each time the record showed that a number of contractions had appeared simultaneously in several parts of the bowel and had each traveled caudad a short distance. In some cases these contractions were probably produced by the action of the irritant drug directly on the muscle as it reached all parts of the gut about the same time.

Occasionally, after giving nicotine, I observed short reverse rushes appearing at one time in several parts of the small bowel, and in some animals, short rushes caudad were associated with short rushes orad. Similar observations were made by Bayliss and Starling, Thomas and Kuntz (75), and Trendelenburg, all suggesting that the drug sometimes flattens the gradient. Other observations, however, indicate that usually this gradient is not much altered.

Incidentally, bathing segments of bowel in strong solutions of atropine had no demonstrable effect on the way in which peristaltic rushes went through.

Effects on the myenteric reflex. I cannot comment on the effect of nicotine on the myenteric reflex, because I have not been able to demonstrate this reflex in the rabbit.

Effect on afferent nerves. The application of pure nicotine to the bowel usually caused the (anesthetized) animal to struggle, indicating that afferent nerves were being stimulated powerfully.

Effects observed in segments of bowel soaked in solutions of nicotine. In a large series of experiments a loop of jejunum or ileum, from 25 to 150 cm. long, was lifted above the level of the fluid in the large tank and dropped into a shallow dish containing a solution of nicotine. Ordinarily I used a dilution of 1:250,000. Nolf concluded that a solution of 1:1,000,000 can be counted on to interrupt synapses in the myenteric plexus of excised gut, but I had to allow for dilution and the washing out of the drug, not only by the circulating blood but by the fluid in the tank. At any rate, with the dosage I used, the affected segment always showed signs of poisoning, often with the rosary-like appearance and sometimes with a temporary weakening of the rhythmic movements. After a segment of bowel had been soaked for two or three minutes, it was dropped back into the tank, recording levers were quickly attached, and water was squirted into the duodenum so that rushes would start there and run down to the region being studied.

It will be remembered that a peristaltic rush consists of a powerful wave of contraction which involves perhaps 15 cm. of bowel. This wave carries ahead of it a column of fluid, a column that can be pushed for long distances through dead bowel procured from another animal or even through lengths of rubber or glass tubing. Knowing this, I was not surprised to find that when rushes approached the poisoned segment of bowel the column of fluid entered at the upper end, and if the segment was not too long or too severely paralyzed, emerged at the lower end. There the fluid stimulated the bowel in such a way that a wave of contraction appeared and went on caudad as a normal rush.

As the rushes traversed a segment of poisoned bowel, there was usually failure of the muscle there to contract, and as a result, much of the column of fluid which would normally have been carried onward was left in the segment. This failure of the muscle to contract in a coördinated way could be seen with the unaided eye, and sometimes it was evident in the records. In normal bowel, the passage of a rush produced a marked rise in the record, with a sharp, steeple-like peak, but when a segment was poisoned, the writing tips of the levers attached to that region were likely to be slow in returning to the base line (Fig. 1, *d*).

As I remarked before, the effect of nicotine on the soaked segments was evanescent, and in many cases, rushes were going through normally again after an interval of from seven to ten minutes. When the local rhythmic contractions were stopped by large doses of the drug they generally reappeared in less than five minutes. The effect of intravenous injections also tended to wear off if the dose was not too large.

Sometimes rushes would continue to seep through the injured segment after one or two soakings in the solution of nicotine, but they could not get through after several soakings, which apparently had had a cumulative effect. Similarly, rushes might get through after the segment had been poisoned with a solution of 1:250,000, but not after it had been in a solution of

1:60,000. Curiously, also, when a small dose of nicotine was injected intravenously, rushes sometimes could still be elicited in the normal bowel, but they would not go normally through a segment which, some time before, had been soaked in a solution of nicotine and had then apparently recovered.

As one would expect, the length of the poisoned segment had something to do with determining whether a rush would get through or fade out. With loops 70 cm. long, some rushes faded out and others did not. In one experiment rushes got through a segment 130 cm. long, and in another they traversed 150 cm. of poisoned bowel. As I said before, if they got through, it was apparently because fluid ran onward, helped probably by a tonic contraction of the distended muscle.

When the soaked segment was severely poisoned, the contraction ring of a rush coming down from above would not enter, and records made of the activity of the segment failed to show any sign of contraction. So far as the unaided eye could detect, the injured bowel was first distended, and then the muscle gradually regained enough tonus to force out some of the fluid that had entered.

Puzzling results ascribable to poor recording apparatus. During the first months of this work I was puzzled to find in most of the records obtained with threads fastened by small wire serrefines to the bowel, signs indicating the passage of a more or less normal wave of contraction. As I have described elsewhere, I finally learned that this was due to defects in the methods of recording, and better apparatus was devised. With the help of a new "distention recorder," the visual observations were shown to be correct, and that in the thoroughly nicotinized bowel there was seldom any wave of contraction following the wave of distention. When a column of fluid entered the upper end of the poisoned segment it was kept going partly by the force applied by the normal bowel orad to the segment, and partly, perhaps, by those contractions of the muscle in the segment which were produced by the stimulus of local distention. Not infrequently the recorders would show what the observer could not see, namely, that a shallow wave of some kind had gone through the nicotinized segment.

It seems certain, then, that nicotine injures some coördinating mechanism which normally causes the intestinal muscle to contract vigorously in the wake of a traveling column of fluid. One can think of its interfering not only with some hook-up of neurones strung along the length of the gut, but also with connections between the mucous membrane and the overlying muscle. Perhaps in favor of this view are the observations of Borchardt, Garry, Raiford and Mulinos (65, 66), and Never, that the application of cocaine or procaine to the mucous membrane of the bowel abolished the usual responses to local distention and tended to interfere with peristalsis. Somewhat against this view is the work of King and Arnold who could not see any sign to indicate that nicotine affects the connections in Meissner's plexus.

I tried to differentiate rushes in normal and in nicotinized bowel by measuring in the graphic records the rate of travel of the wave, but I could not find any characteristic difference.

Painting a segment with nicotine. Painting a segment with nicotine did not work as well as soaking it in the solution. In one instance, the painting of a short segment with a 1:250 solution of the drug almost paralzyed the whole gut. Either a large amount of the poison had passed into the blood stream or else there was a powerful reflex inhibition.

Effect of nicotine on long nervous tracts and nerve endings. What I call "long-distance nervous conduction," which correlates activities in all parts of the bowel, was not impaired even by lethal doses of nicotine. By cutting away the mesentery from a heavily nicotinized segment of bowel and stimulating at a point orad, I could show that long-distance conduction can take place through such a badly poisoned loop. I found also that a stimulus coming from a distant part of the gut could affect the muscle in a poisoned segment, showing that not only the nerve fibers but also the endings in the muscle must be highly resistant to the action of the poison.

In one remarkable experiment in which a rush occurred while the animal was severely poisoned by an intramuscular injection of nicotine from a freshly opened bottle, the wave was unable to enter a segment which had previously been soaked several times in a dilute solution of the drug, and yet, as the rush swept down the upper part of the bowel, the muscle in the poisoned segment showed a decided anticipatory increase in tonus such as is characteristic of the approach of a big wave in normal bowel.

What looked like the result of a persistence of function in the long conducting tracts and in the nerve endings connected with these tracts was observed in several rabbits in which, after severe poisoning of the whole animal, there appeared simultaneously throughout the bowel a series of powerful contractions. According to Dixon such synchronous contractions of the whole bowel have been observed in men poisoned by nicotine. Perhaps it is this type of spasm with superimposed traveling waves which produces the diarrhea seen in some patients poisoned with nicotine. Theoretically, if peristaltic rushes are abolished by the drug, in man as in animals, there should not be any diarrhea. Perhaps, however, the colon is stimulated to contract more or less as a whole and thus to empty itself.

A gradient of susceptibility along the bowel. In a number of animals, injected with large doses of nicotine, it was noted that the rhythmic activity ceased at the oral end of the bowel when it was still present at the caudal end. As recovery took place, the rhythmic contractions appeared first at the caudal end and slowly spread orad. In one experiment it was an hour before the returning rhythmic contractions reached the duodenum.

Rate of travel of peristaltic rushes in nicotinized bowel. As I have already said, I could seldom see any deviation from normal in the rate and regularity of progress of the rushes which could sometimes be elicited after the giving of nicotine, but sometimes they were unusually fast.

COMMENT

Nicotine, even in moderate concentrations, seems usually to paralyze some part of the nervous mechanism of the bowel, probably a synapse. It seems also to put a stop to the rhythmic functions of certain ganglion cells. In massive doses it is probably a general protoplasmic poison which can injure the muscle fiber. Strangely, in such large doses it does not block conduction in the nerve fibers, or in the

nerve endings in the muscle, or in the synapses between extrinsic nerves of the bowel and the myenteric plexus.

As I have said, the discovery by Berkson (7, 8, 9, 10, 11), and later Puestow, that nicotine stops the "action current" while it tends to leave the rhythmic contractions with a slower rate and a larger amplitude, suggests that, much as in the heart of Limulus, so in the bowel, impulses originating in ganglion cells modify the rhythm of the muscle. Curare had much the same effect as nicotine on the electro-enterogram, and ephedrine had a deleterious effect on both the electrical and the mechanical record (Berkson (8)). Epinephrine stopped the muscular activity but left the "action currents" (Alvarez and Mahoney, Berkson (7), Puestow, Castleton).

Although it seems probable that peristaltic rush is largely dependent on a synaptic nervous mechanism, many of my observations do not fit perfectly with this view. Too often what appeared to be normal rushes ran through a bowel severely poisoned by either nicotine or long continued anoxemia. As I have pointed out in an article on anoxemia, the easiest way out of this difficulty would be to assume that the puzzling waves were all abnormal, but I cannot do this because, in so many instances, I could not see anything wrong either with the unaided eyes or with the help of graphic records. Unfortunately for the experimenter, there are several mechanisms which can serve to keep rushes going, and some can produce a normal-looking wave.

In a number of most interesting and thought-stimulating articles, Nolf has reported studies with nicotine which indicate that in the chicken, Auerbach's plexus consists primarily of a chain of neurones running the length of the bowel and connected with valve-like synapses which permit conduction and peristalsis only in the caudad direction. Experiments indicate that the vagal and the preganglionic sympathetic fibers are connected by synapses with this primary chain of neurones, while the postganglionic sympathetic fibers go directly to the muscle. There are reasons for believing also that in the chicken there is a second group of neurones interposed between those of the longitudinal conducting chain and the muscle fibers of the gut. So far as my experiments go they do not suggest the presence of similar neurones in the myenteric plexus of the rabbit, but I have not yet had the opportunity to repeat Nolf's experiments exactly as he performed them.

SUMMARY

An attempt was made through the use of nicotine to learn something about the structure and functions of Auerbach's plexus and about the mechanisms underlying peristaltic rush. Unfortunately there still are doubts as to the exact way in which the drug affects the nervous system. The effects obtained vary somewhat with the dosage used.

Most susceptible of all structures seem to be certain synapses in Auerbach's plexus, and the ganglion cells. The immunity of the vagal nerve endings to large doses of nicotine was confirmed. Almost insusceptible to nicotine were the nerve fibers and their endings in the muscle.

Conduction over long stretches of bowel seemed actually to be improved, so that the gut sometimes contracted as a unit.

Nicotine improved the amplitude of the rhythmic contractions of the intestinal muscle; it made them more regular, and usually slowed their rate. Only in the largest doses did it temporarily stop them. The irritability of the muscle was almost unaffected even by the largest doses of nicotine. The nicotinized bowel commonly presented a beaded appearance.

The tendency of nicotine to interfere with peristaltic rush was confirmed, but this effect could not always be demonstrated. The difficulty may have been due at least in part to the fact that there are several mechanisms by which a rush can be forwarded. A segment of bowel poisoned by nicotine did not empty itself caudad as well as did normal segments. Nicotine seemed to interfere with the mechanism which connects the muscle to the underlying mucosa. The effects of nicotine wore off quickly.

There were indications of a gradient of susceptibility to nicotine along the small bowel, with the oral end more susceptible to injury than the caudal end.

Nicotine did not seem to interfere with peristalsis in the stomach or colon.

It was found that nicotine can so decompose that, while retaining most of its characteristic toxic effects, it loses much of its ability to interfere with peristaltic rushes.

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The Management of Strangulated Hemorrhoids*

By

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THIS controversial subject is still the cause of much debate, after these many years. Whether to operate early or to delay until the active inflammation has subsided is still as undecided, in some quarters, as it was in William Allingham's time. The remark of N. J. Kilbourne (1) when discussing prolapsed, strangulated, gangrenous hemorrhoids that "Such cases are not usually operated on by competent proctologists in this stage" serves to show the attitude of some physicians. That such a view is not correct I

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have been able to determine by interrogating the competent proctologists of the United States and Canada.

DEFINITION

The term hemorrhoid means, of course, varicosities in the lower rectum, and not perianal hematomas. The various descriptive terms, such as prolapsed, thrombosed, strangulated, and gangrenous hemorrhoids refer merely to pathological changes and to changes in position of the lesion. The condition may or may not be accompanied by perianal hematomas, and anal edema may be much or little. There is one common finding in strangulated hemorrhoids and that is thrombosis of the arteries, veins and capillaries making up the hemorrhoid.

ETIOLOGY AND PATHOLOGY

It was formerly thought that thrombosed, prolapsing hemorrhoids were due to strangulation, produced by the sphincter muscles, but this idea is gradually giving way to the more tenable theory that the resulting pathology is one of trauma. The extrusion of a hard stool, or perhaps severe diarrhea, prolapses the hemorrhoids breaking the intima, and thrombosis results. The natural sequence then is edema, cellular infiltration, inflammation, ulceration and frequently gangrene. Strangulation does not enter into the picture at all, as noted by F. C. Smith (2). Inserting the finger into the rectum of one of these cases shows that the sphincters themselves offer no resistance.

With this pathology in mind, it would appear to me that it is just as essential to excise this tissue at the earliest possible moment, as it is to excise a perianal hematoma at once, which latter procedure is universally accepted, I believe. Delay in instituting surgery serves to prolong the pain unnecessarily and increases the likelihood of sepsis.

FEAR OF EMBOLISM

The danger of embolism is often mentioned, and this is no doubt a real danger when a crushing clamp is used, or when the anesthesia consists of local infiltration. In the fatal cases I have investigated the clamp and cautery or local infiltration was used. Clean surgery by prompt excision of the masses, under a block anesthetic, either spinal or caudal, or, if required, a general anesthetic, helps to avoid this danger and is a safe procedure to be followed in thrombosed hemorrhoids. Some vessels will require ligation, but this is easily accomplished when the hemorrhoids have been removed.

An embolic death may follow a simple hemorrhoidectomy as well as after an operation on thrombosed piles, and the menace is not confined to proctology, as orthopedists and gynecologists will testify.

FEAR OF LIVER ABSCESS

Another danger that is given considerable thought is the likelihood of liver abscess, or a general blood stream infection, following surgery on thrombosed or gangrenous hemorrhoids. W. B. Gabriel (3) in his book has this to say, "Septic internal piles should be treated on palliative and antiseptic lines. When the piles are perfectly clean, a decision can be made as to what further treatment, if any, is required." Yet on page 30 of this same book, we find this sentence. "The process is almost invariably well localized, and in spite of the theoretical dangers of septic pylephlebitis and portal pyaemia, I can recall only one death from a sloughing haemorrhoid." This death in a patient who was not operated upon shows us that liver abscess may occur in the absence of hemorrhoidal surgery as well as following such surgery. Necrosis, therefore, is no contra-indication to the removal of these hemorrhoids, provided it is done without clamps and without local infiltration. Lockhart-Mummery (4), with whom Gabriel was associated as an assistant for some time, writes in his most recent book, as follows: "I have always made it a practice to operate at once upon sloughing and strangulated piles, unless some other contra-indication existed. The result in all cases has been an immediate relief of pain; and as a rule the patient has been quite well again in a fortnight or three weeks, and at the same time cured of his piles. If one waits until all sloughing and inflammation have subsided before doing the radical operation, the total time before the patient is well is nearer five or six weeks." "I have never seen any ill-effects follow immediate operation upon sloughing piles, and, on the other hand, I am sure that the patient is saved much trouble and pain by immediate operation."

FEAR OF STENOSIS

Still another reason given for delayed operation is the inability to judge the amount of tissue it is necessary to remove. It is a bit disconcerting to be confronted with a patient having large clumps of thrombosed hemorrhoids protruding from the anal canal. My experience in these cases has been very satisfactory. The convalescent period has frequently been shorter than following an uncomplicated case. Experience, of course, is the guide one needs to reach a decision as to what sort of a plastic or repair operation is required in the case at hand.

CASE REPORT

A typical case report follows: F. R. S., male, 51 years old, a packing house employee, was brought to the hospital by his doctor, with this history: Rectal bleeding and protrusion for at least twenty years. For the past few days piles have been out and he is unable to replace them. When the piles were first protruded, one was bleeding quite badly, and his doctor ligated it with black silk. I saw the patient at the hospital and found a lobulated mass as large as a small orange prolapsed from the rectum. The ligated pile was gangrenous and gave off the characteristic odor. The patient was suffering intense pain. He was sent to surgery immediately and under spinal anesthesia all thrombotic and gangrenous piles were excised. No clamps were used at any time. The bleeding vessels were ligated when necessary. He entered the hospital August 5, 1935, dismissd from the hospital August 9 and discharged from my care August 23. He had the largest collection of prolapsed, thrombosed hemorrhoids I have ever seen.

I have recently obtained the views of the surgeons of the American Proctologic Society concerning this vexatious problem. Of 116 replies to my questionnaire 76 operate promptly upon acute strangulated hemorrhoids while 38 do not, and two follow no predetermined plan.

It is interesting to note the trend away from the clamp and cautery, as shown by the choice of operation from the 76 operating early. Only eight chose the clamp and cautery, while 65 use some form of a modified ligature operation, and three had no preference. It would appear that if there ever was a time when the clamp and cautery was especially dangerous it would be in the presence of thrombosis. Quite a

number of the surgeons volunteered the information that they *never* use the clamp and cautery.

The choice of anesthesia assumes as great importance, from the standpoint of safety, as does the type of operation. There are 18 who use local infiltration, the big majority use block anesthesia, and a few general. If the infiltration is made at a considerable distance away from the thrombosed area it may be a fairly safe method. If not away from the area the procedure may be extremely dangerous. This view is held by a big majority of the surgeons as shown by their choice of block anesthesia.

A few replies to the questionnaire follow: Dr. Louis J. Hirschman prefers the ligature operation with caudal anesthesia. He says: "Knowing that a blood clot forms an excellent medium for the culture of pyogenic organisms in this region thrombosis is an indication for immediate removal."

"Knowing that strangulation means necrosis and even when hemorrhoid is reduced means recurrence, immediate removal is also mandatory."

Dr. Curtice Rosser uses the ligature operation, always under a block (spinal or caudal) or general anesthesia, never under infiltration. He says: "I find that it is always possible to discover normal tissue at the *base* of the strangulated pile and if local injection of chemicals and trauma to the pathologic tissue is avoided at operation, I believe there is *less* danger in the removal of the pathology than in awaiting further extension. I used the clamp and cautery for some years in this situation, but decided there was some danger of trauma with the clamp."

Dr. Frank C. Yeomans uses the clamp and cautery operation and uses low spinal anesthesia with a small dose. He says: "My results in several such cases have been very satisfactory." In his book (5) we find the following: "When the sphincter is tight and the protrusion not replaced, thrombosis of the vessels and gangrene frequently ensue. Sloughing then occurs and spontaneous relief may be obtained, but at the expense of several weeks of needless pain, suffering and disability. Prolonged ulceration, abscess, or a fistula may be sequelae. Under these circumstances, when the situation is fully explained to the patient and there is no other contra-indication to operation, he will usually accept immediate operation, which is the proper procedure for strangulated, sloughing piles. Relief is immediate, the hemorrhoids are cured, and no complications, other than those encountered in a simple hemorrhoidectomy, ensue. To limit the possibility of infection, the clamp and cautery is the operation of choice."

The 38 surgeons advising delay before instituting surgery in strangulated hemorrhoids gave as their reasons; fear of embolism, blood stream infection or liver abscess, and fear of stenosis if too much tissue is removed. They advocated various methods of palliation, chiefly rest and hot moist compresses.

One of the most interesting discussions that I read on this subject was that of N. L. Blumental (6), Director, Surgical Division of Trekhgorny Hospital, Moscow, U.S.S.R.

He recounted the dangers of the conservative treatment of strangulated piles, and emphasized the likelihood of the condition not remaining localized, with embolism and pyemia imminent. He then decided to break away from the generations-old attitude of merely standing by while the nurse recorded exquisitely painful as well as dangerous defecations, the while applying hot water compresses. In a series of cases operated upon by excision, without clamps and without anal dilatation, under general anesthesia, his results were so good that he recorded them in a paper which should be read in its entirety.

The important thing to remember is that we all want to get our patients well. However we should not close our minds to any advances in surgical therapy which tend to hasten this end. A procedure which brings about a worth-while reduction in human suffering, while at the same time eliminating the hazards of watchful expectancy, should be utilized.

SUMMARY

An attempt is made to bring order out of chaos in the therapy of strangulated hemorrhoids. Following a description of the condition, the etiology and pathology are taken up in turn. The alleged dangers of early operation are cited, and the reasons for these dangers are given. Quotations are taken from well-known text books on proctology. A questionnaire was devised and submitted to members of the American Proctologic Society for their opinions on this vexing problem. These questionnaires were tabulated, and quotations made therefrom. One case history is given.

CONCLUSIONS

Strangulated, thrombosed, sloughing, and gangrenous hemorrhoids should be operated upon promptly.

The danger of embolism or liver abscess is greater in those cases not operated upon, than it is in those cases operated upon under block anesthesia, without clamps, and without anal dilatation.

The preponderance of opinion among the surgeons of the American Proctologic Society favors this procedure.

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A Collapsible Indwelling Nasogastric Tube

By

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A METHOD has been devised for using a collapsible thin rubber tube for the instillation of medication and food into the stomach through the nose. A need for such a tube was encountered in the treatment of peptic ulcer by the continuous administration of colloidal aluminum hydroxide (1). The Levin nasal catheter which, in this treatment, must be left in for several days, presented a number of difficulties. When the larger sized catheters were used, many patients complained of irritation and soreness of the nose and throat caused by the stiff rubber tube. Even when the smallest tube was used, there was still considerable irritation in some instances, and also the colloidal aluminum hydroxide, even in diluted form, tended to collect in the narrow lumen, causing obstruction of the flow into the stomach.

These difficulties were overcome by using a thin rubber tubing (Penrose Latex) one-fourth inch in diameter and 30 inches long, of the type used for cigarette drains in surgical cases. This tube is not sufficiently rigid to pass through the nose into the stomach, so an obturator has to be used. This is made from silk-worm gut suture by tying two 15-inch lengths together with a piece of thread. Other rigid suture material might also be used. The suture gives the tube just enough rigidity to allow it to be forced through the nostril and into the esophagus. A small loop is made at the distal end of the silk-worm gut suture and tied with thread, so that the sharp end can not injure the mucous membrane. The suture is inserted into the lumen of the tube as an obturator, which stops about one inch from the distal end. This free end of the soft tubing is folded on itself to prevent protrusion of the suture material while the tube is being passed. After the tube reaches the stomach, the free end of the tube straightens out again.

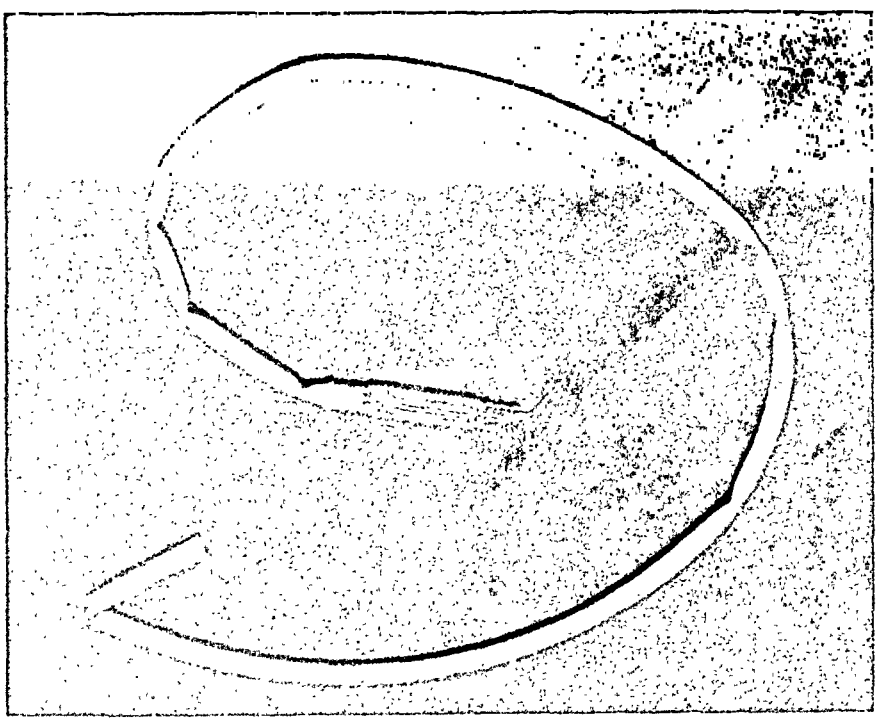


Fig. 1. The thin-walled nasogastric tube with silk-worm gut suture obturator in place. Note that the obturator prevents sharp kinking of the tube.

The technic of passing the tube is as follows: The outside of the cigarette drain is first lubricated by dipping the length to be passed in mineral oil. The tube must be grasped tightly so that the tube and the obturator are passed together through one of the nostrils until the pharynx is reached. The patient is asked to drink water through a straw while the remainder of the tube is pushed down slowly through

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the esophagus into the stomach. The obturator is left in the lumen to prevent sharp kinking of the thin-walled tube.

The proximal end of the thin tube is connected to another rubber tube by a glass connection. The obturator at this end is permitted to extend into the glass connecting tube a short distance to preclude any kinking at the junction of the glass tube and the cigarette drain. A small strip of adhesive holds the tube against the upper lip to keep it from slipping out.

This type of tube can not be used for siphonage because any suction causes it to collapse. This has proved an additional advantage in the continuous instillation of aluminum hydroxide into the stomach. With the Levin tube, whenever the level of the patient's stomach is elevated, as when he sits up, there is suction of the stomach contents into the air-tight gravity bottle. The collapsing of the thin tube under such circumstances allows fluid to flow into the stomach but does not permit a back flow or suction. Hence this thin tube has a definite sphere of usefulness in the instillation of food or any other material into the stomach when siphonage of stomach contents is undesirable. The lumen of this tube, which is much larger than that of the ordinary thick-walled gastric tube, allows a free flow of any thick material.

This tube has been used on many patients and not one of them has complained of discomfort or irritation while the tube was in place for ten days or more. There is no interference with eating or drinking, and, in most instances, the patient is scarcely conscious of its presence. In one patient with an old fracture of the nose this collapsible tube was especially useful. His nasal passages were too small to permit passage of the smallest Levin tube, but admitted the thin-walled tube with no difficulty.

The advantages of a thin-walled tube in the instillation of material into the stomach are (1) irritation of the nose and throat or esophagus is prevented, (2) the tube is so soft that there is no danger of any injury to any lesion of the stomach, (3) there is no possibility of back flow or suction of stomach contents and (4) because of its large lumen there is no obstruction by particles of food.

This method of instillation of medication or food into the stomach is convenient and immediately available for use, because it simply consists of a new adaptation and use of materials already at hand. In addition to its service in the treatment of peptic ulcer, it is also useful in cardiospasm and in carcinoma of the esophagus to allay superimposed irritation. It is of value in any case in which prolonged intubation is necessary, for it has a distinct advantage over other types of tubing in protecting the tissues of the body from irritation and trauma.

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The Incidence and Permanence of Unexplained Gastric Anacidity in the Rhesus Monkey After Histamine and Mecholyl, with Hemotologic Studies*

By

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and

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A STUDY of the incidence and permanence of gastric anacidity in the monkey is of significance because of the close relationship of this animal to man.

Polland (1) using histamine and Vanzant (1) using a test meal found a similar percentage of incidence of anacidity in the human. The percentage of frequency of anacidity in the human varied with the age and sex. In their series the percentage incidence of anacidity between the ages of 20-39 years was male 3.2, female 6.4; 40-59 years male 12.2, female 18.9; over sixty years male 30.6, female 23.3. The average incidence of the entire series was 14%; male, 12.0%; female, 16.2%. Dietrick and Shelby (2) found free acid in response to histamine in every case in a series of 14 children (ages 4-14 years). Polland and Bloomfield (3) determined the pepsin concentration of the gastric juice from 8 patients with complete anacidity after histamine. In only one case was there no trace of pepsin, another showed an increased concentration of pepsin while the other six all showed low concentrations of pepsin. Bloomfield and Polland (4) in their experience have found that true anacidity is permanent and are of the opinion that the observations on the return of normal acidity, after long periods of absence, must be looked on with some skepticism, because they are based upon test meals, and not upon the results of histamine stimulation.

METHODS

Forty-five healthy Rhesus monkeys (macaca mulatta) (23 males, 22 females) varying from one to six years of age were employed in this study. The monkeys have been divided into three age groups, youthful, adolescent and mature, according to their size, weight and sexual development. All the monkeys have been in our laboratory for from eight months to six years. They have been maintained in a state of good nutrition upon a varied diet consisting of milk,

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potatoes (raw and boiled) bread, carrots, lettuce, bananas, oranges, apples and peanuts.

Gastric analysis was performed upon monkeys fasted for 24 hours. A Rehfuss tube (minus the olive) was passed into the stomach and the fasting contents were removed; the stomach was washed with distilled water and emptied. The monkeys then each received 0.5 mg. histamine (ergamine acid phosphate) subcutaneously. If free acid failed to appear in the gastric samples, the dosage of histamine was increased to 1.0 mg. Gastric samples were taken at 30, 45 and 60 minute intervals after each injection and analyzed for free acid (p-dimethylaminoazobenzene) and bile (naked eye).

Eight to ten gastric analysis were made over a period of eight months upon those monkeys which did not respond to dosages of histamine up to 1.0 mg. A qualitative assay for pepsin (Mett tubes) and rennin (milk coagulation) was made on the gastric juice of the anacid monkeys. Erythrocyte, hemoglobin (Newcomer) and hematocrit determinations were made upon all of the monkeys.

RESULTS

The viscid, mucoid fasting contents of the stomach were scanty, never contained free acid and but little total acid.

Table I shows that 8 of the 45 monkeys (17.7%) did not have free acid in the gastric samples taken at 30, 45 and 60 minute intervals after subcutaneous injections of 0.5 mg. and 1.0 mg. of histamine. In our entire series anacidity in the male was 13.0%; female, 22.7%.

TABLE I

Incidence of gastric anacidity after histamine in the normal Rhesus monkey

Age	Weight lbs.	Sex	No. Animals	Gastric Anacidity Histamine 0.2 mg. No.	0.5 mg. 1.0 mg. %
Youthful	3.5-4.5	Male	8	2	25
(12-18 Mo.)		Female	6	1	16.6
Adolescent	4.5-6.0	Male	3	1	33.3
(18-30 Mo.)		Female	9	2	22.2
Mature	6.0-10.3	Male	12	1	8.3
(30-72 Mo.)		Female	7	1	14.2
Total			45	8	17.7

Table II shows that the anacidity persisted in the eight monkeys for from one to five months. Gastric pepsin and rennin however were present in all cases. Regurgitation of bile and intestinal contents did not occur.

On February 8, 1937, free acid was secreted by four of the eight anacid monkeys after 0.3 mg. of Mecholyl (acetyl B. Methyl choline chloride) given in three subcutaneous injections (0.1 mg. each, 15 minutes apart). This dose of Mecholyl, given in the manner indicated, stimulates gastric secretion in dogs (4). On February 10, 1937, six of the anacid monkeys secreted free acid in response to 1.0 mg. of histamine also given in three injections (0.33 mg.) at 15 minute intervals. On March 20, 1937, all the anacid monkeys except No. 35 secreted free acid following one injec-

TABLE II

On the permanence of gastric anacidity after histamine and mecholyl in normal Rhesus monkeys

Monkey	Age	Sex	Enzymes		(H = Histamine)				Free Gastric HCl				(M = Mecholyl)		
			Pepsin	Rennin	9/2 H	9/8 H	9/18 H	1/5 H	2/5 H	2/8 M	2/10 H	3/20 H	4/2 H	4/14 M	4/29 H
5	Mature	Female	+	+	—	—	—	—	—	+	+	+	+	+	+
10	Adolescent	Female	+	+	—	—	—	—	—	—	—	+	+	+	+
12	Mature	Male	+	+	—	—	—	—	—	—	+	+	+	+	+
27	Adolescent	Female	+	+	—	—	—	—	—	+	+	+	+	+	+
28	Youthful	Male	+	+	—	—	—	—	—	—	—	+	+	+	+
29	Youthful	Female	+	+	—	—	—	—	—	—	+	+	+	+	+
34	Youthful	Male	+	+	—	—	—	—	—	+	+	+	+	+	+
35	Adolescent	Male	+	+	—	—	—	—	—	+	+	—	+	+	+
39	Adolescent control	Female	+	+	+	+	+	+	+	+	+	+	+	+	+
40	Adolescent control	Female	+	+	+	+	+	+	+	+	+	+	+	+	+
41	Adolescent control	Female	+	+	+	+	+	+	+	+	+	+	+	+	+

tion of 0.5 mg. of histamine. In three subsequent gastric analysis at 2 week intervals, all of the anacid monkeys secreted free acid following single subcutaneous injections of 0.5 mg. histamine and of 0.15 mg. mecholyl.

Blood studies showed that none of the above anacid monkeys were anemic at the time that the analysis were made.

One of our monkeys (No. 7) had an anacidity and only 9.05 gm. % hemoglobin. After the hemoglobin was brought up to 12.50 gm. % by the oral administration of iron salts, free acid was found in the gastric samples in response to histamine.

Because our series of 45 monkeys is considerably larger than any upon which hematologic studies have been reported and because of our correlation of the blood picture with the age and sex of the monkey, we shall include our hematologic findings in this paper. The largest series occurring in the review of the literature by Hall (5) is that of Krumbhaar and Musser, who in 14 monkeys found average values of 5.985 million erythrocytes and 85.15% hemoglobin. The average ranges of erythrocytes of the various authors varied from 4.648 to 6.252 million and the hemoglobin from 60 to 85.45%. In a series of 11 normal Rhesus monkeys Bussabarger and Ivy (6) found a mean erythrocyte value of 6.200 million and a mean hemoglobin value of 12.86 gm. %, the mean hematocrit value being 47.64.

TABLE III

Blood picture of normal macacus Rhesus monkeys

Age	Weight	Sex	No. Animals	No. Determinations	R.B.C.	Hb per 100 c.c.	Hematocrit
Youthful	3.5-4.5	Male	8	16	5.270	11.84	47.2
(12-24 mos.)		Female	6	12	5.169	12.42	45.9
	Average		14	28	5.193	12.07	45.6
Adolescent	4.5-6.1	Male	3	6	5.456	12.25	45.8
(24-57 mos.)		Female	5	10	5.219	11.56	41.2
	Average		17	34	5.300	11.79	43.5
Mature	6.5-12.5	Male	13	26	5.378	12.73	42.8
(57-72 mos.)		Female	7	14	5.333	11.97	40.4
	Average		20	40	5.511	12.35	41.9

*Newcomer method.

Table III shows that a sex difference in the blood picture was not found and that the values fall within the same range in youthful, adolescent and mature Rhesus monkeys. The average values and ranges of the determinations are shown in Table IV. It is interesting to note that the average values given by different authors upon smaller series fall within our range.

TABLE IV

Average blood picture for 45 normal macacus Rhesus monkeys

Determination	No. of Determinations	Average	Range
Red Blood Count	99	5.410	(4.756-6.064)
Hemoglobin (Newcomer)	99	12.27	(9.64-16.32)
Hematocrit	99	47.8	(31.0-59.5)

DISCUSSION

In spite of our small series it is interesting to note the close comparison of the percentage incidence of anacidity in monkeys, 17.7% (male 13.0%, female 22.7%), with the percentage incidence of anacidity of the entire series of Polland and of Vanzant, 14% (male 12.0%, female 16.2%). The correspondence is striking.

The presence of gastric enzymes (pepsin and rennin) in anacid monkeys confirms the observations of Polland and Bloomfield on the human.

Our results on the monkey do not agree with their observation that true anacidity is permanent because our monkeys showed a true unexplained anacidity to histamine upon repeated gastric analysis over a period of five months and then within a period of five days six of the anacid monkeys secreted free acid after the administration of mecholyl, a drug which from the available evidence is a powerful parasympathetic stimulant. Thereafter all of the eight anacid monkeys secreted free acid in response to histamine and to mecholyl over a period of three months. A recurrence of anacidity occurred in one monkey (No. 35) on one occasion only (March 20, 1937).

Since all of our anacid monkeys were in good health and were not anemic, the anacidity was not due to anemia as has been brought out by Apperly (7). We did have one monkey in which the anacidity disappeared after the anemia was corrected.

The abruptness of the appearance of free acid following the administration of mecholyl in all of our monkeys, formerly anacid to histamine, leads us to believe that this powerful parasympathetic stimulant may have awakened a latent or dormant acid secretory mechanism. This suggests that anacid human subjects should be injected with the small doses of mecholyl to ascertain if responsiveness to histamine will appear. However, our studies do not rule out the possibility of a seasonal variation, which is important, if true.

CONCLUSIONS

1. The incidence of gastric anacidity after hista-

mine in a series of 45 healthy Rhesus monkeys was 17.7% and was higher in the female (22.2%) than in the male (13.0%).

2. Gastric pepsin and rennin was present in the gastric contents of all of the anacid monkeys.

3. The unexplained gastric anacidity after histamine lasted for from two to five months and disappeared suddenly following administration of mecholyl.

4. Subcutaneous injections of mecholyl caused the secretion of free acid in normal monkeys and in eight monkeys which have been anacid to histamine for five months.

5. Hematologic studies revealed no age or sex difference in the blood picture of our monkeys.

6. These observations in monkeys indicate that the effects of mecholyl in anacid human subjects should be studied.

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A Method of Determining and Recording Human Intestinal Motility*

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IT is generally admitted that we do not as yet possess a valid and acceptable method for assaying cathartics. The attempts thus far made have been largely directed in noting the consistency of the stools, in weighing them, or in counting their number in animals or in human beings after the taking of the drug. It may well be doubted whether this method of study will lead to conclusions of marked therapeutic value. The term "constipation" has no scientific meaning and should give place to the term "colon stasis," and the relief of this stasis should be the aim of therapy, rather than the production of a greater number of bowel movements. Even numerous and liquid evacuations may not affect the actual seat of

*From the Laboratory of Pharmacology and Therapeutics of the College of Medicine, University of Illinois, and the Chicago State Hospital for the Insane.
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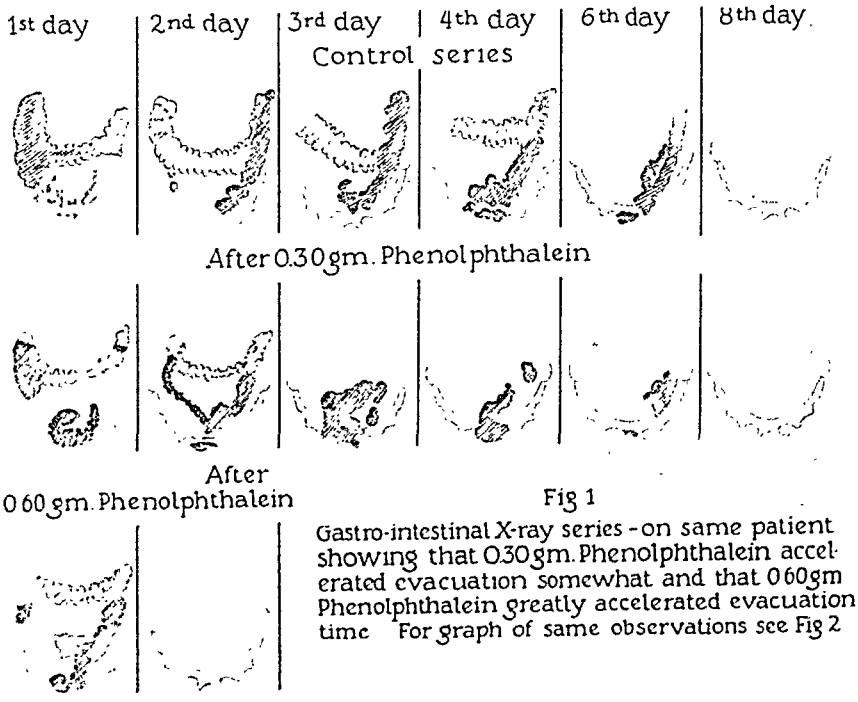


Fig 1

Gastro-intestinal X-ray series - on same patient showing that 0.30 gm. Phenolphthalein accelerated evacuation somewhat and that 0.60 gm Phenolphthalein greatly accelerated evacuation time For graph of same observations see Fig 2

Fig. 1. *Typical X-ray Gastro-Intestinal Series*, Secured from One Individual: First row: Control Series; Second row: After 0.30 Gm. Phenolphthalein Series; Third row: After 0.60 Gm. Phenolphthalein Series. It will be seen that while the 0.30 Gm. dose lessened the cecal evacuation time, it did not very markedly lessen the total evacuation time. The 0.60 Gm. dose caused great acceleration in total evacuation time.

the colon stasis or relieve the patient of the symptoms thereof.

It must be remembered that the colon is a large complicated organ which may roughly be divided into several functional departments:

(1) The cecum and ascending colon, the chief func-

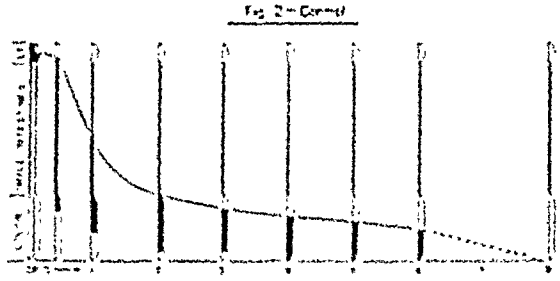


Fig. 2. *Control Series.* Curve secured in interpretation of the X-ray gastrointestinal series shown in Fig. 1

tion of which is to retain the digesting material thrown into it from the small intestine until much of the fluid has become absorbed from its contents. That the consequent reduction of the bulk of the contents is an important function of this part of the intestine is evident from the fact that the cecum holds approximately four times the volume contained in an equal length of any other colon segment. It is the most distal portion of the actual digestive apparatus. Retention occurs normally; and abnormal retention, or stasis, is very common. It is likely to be detrimental to health when it occurs to a marked degree.

(2) The transverse colon is that part in which the inspissation of the contents is completed and the formation of fecal material begun.

(3) The descending colon finishes the formation of feces and becomes completely emptied with a "peristaltic bowel movement." It might be considered the colon "shipping department."

(4) The sigmoid colon, which is equal in length to any one of the other portions of the colon, with the rectum, retains the feces until evacuation.

(5) The rectum should normally be practically

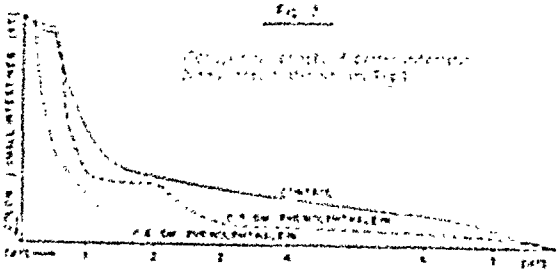


Fig. 3. Comparison of curves representing tail end of column in the roentgenintestinal X-ray series shown in Fig. 1: A, Control series, B, 0.30 Gm. phenolphthalein series, C, 0.60 Gm. phenolphthalein series.

empty excepting just before a bowel movement, as the presence of a considerable amount of material in it should excite the act of defecation.

Though admitting that it is *merely schematic*, it is believed this interpretation of the functions of the anatomic divisions of the colon has didactic value. It is, of course, admitted that the proximal colon is a functional unit which extends to the junction of the right and middle third of the transverse colon. It is

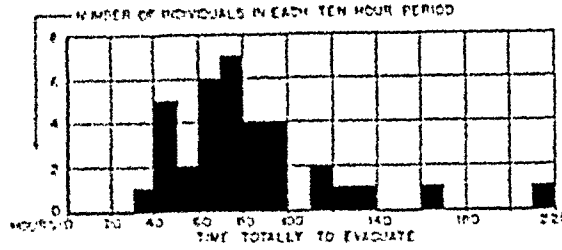


Fig. 4. *Control Cases.* Frequency distribution graph of the time required totally to evacuate the gut, using the average of the two control observations on any one individual.

also admitted that the various segments of the colon have compensatory relations to each other.

THE PROBLEM

Cathartics must be studied from the standpoint of determining where in the colon their action is chiefly exerted and patients suffering from constipation must be examined to determine in what portion of the colon the stasis occurs, so that the patient may be fitted with the cathartic he really requires; that is, the one which will best correct the functional abnormality.

In spite of the fact that humanity has been using cathartics from time immemorial, it may seem remarkable that the scientific study of the action of cathartics in health and in disease has barely been commenced. The chief reason for this is that an efficient means—the roentgen-ray—by which such study may be accomplished, has been put into our hands but a few decades ago. Thus far, roentgenologists have been largely concerned with the study of anatomic rather than functional abnormalities. The

Fig. 5. Control Cases.

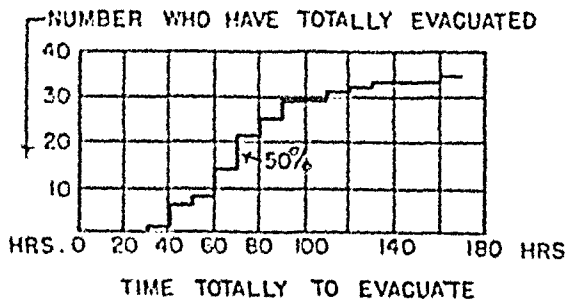


Fig. 5. *Control Cases.* Summated data for same group of tests shown in Fig. 4, showing that the most probable (50%) time for total evacuation of gut is about 70 hours.

great expense of such a study is, no doubt, an additional impeding factor.

At least four steps must be taken to remedy our deplorable ignorance of the nature and the treatment of colon stasis.

First, there is a crying need of a large and comprehensive series of control observations in normal individuals. These observations should include at least two gastro-intestinal X-ray series upon each person,

Fig. 6. Control Cases.

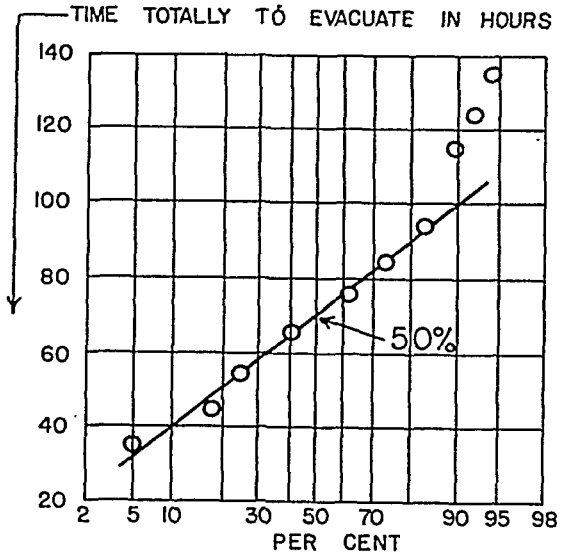


Fig. 6. *Control Cases.* Same data as shown on Fig. 4 and Fig. 5, plotted on "probability paper" after the number of cases has been reduced to percentages. The 50% ordinate intersects the time abscissae at about 70 hours.

in order to obviate errors due to the normal variations encountered in the individual. The cases might have to be differentiated under such headings as:

Colonic Motor Function:

(a) in individuals with and without visceroptosis

(b) in persons of sedentary habit and in those doing manual labor

(c) in habitual consumers of residue-high diet and of residue-low diet

Fig. 7. Phenolphthalein 0.30 Gm. Cases.

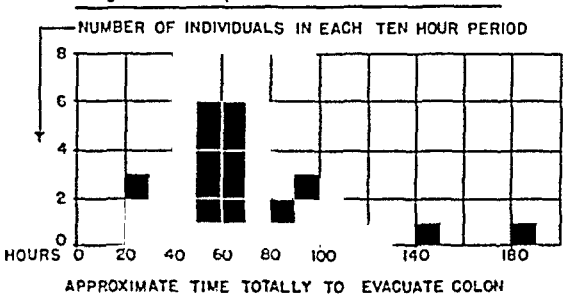


Fig. 7. *Phenolphthalein 0.30 Gm. Cases.* Gut evacuation time shown on frequency distribution graph.

(d) in the phlegmatic and the emotional, etc.

Secondly, once such a control study is available, it could be decided when abnormal retention of colon contents, or colon stasis proper, can be said to exist. It would then—and only then—be possible to study the clinical significance of the different types of colon stasis encountered in patients.

Thirdly, all the important cathartics should be studied as to their effect upon "normal" individuals, and then upon the several classes of diseased individuals to which they are to be applied.

Fig. 8. Phenolphthalein 0.30 Gm. Cases.

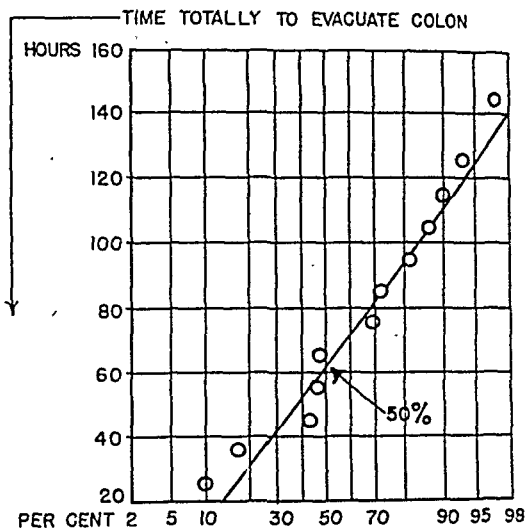


Fig. 8. *Phenolphthalein 0.30 Gm. Cases.* Gut evacuation time plotted on probability paper, showing that the most probable mean is at 62 hours.

Fourthly, when a certain form of harmful colon stasis has been encountered, it should be scientifically fitted with the proper evacuant procedure, be this a regimen depending on diet or drug, exercise, or enema, physical therapy or surgery.

Finally, having roentgenographically identified the nature of the harmful colon stasis, there should be no cessation in treatment until a subsequent X-ray examination shows that the abnormality has been corrected by the treatment chosen.

Fig. 9. Phenolphthalein 0.60 Gm. Cases.

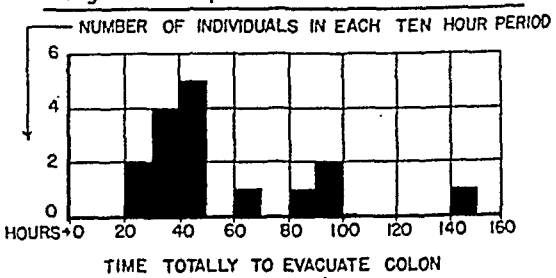


Fig. 9. *Phenolphthalein 0.60 Gm. Cases.* Gut evacuation time frequency graph in subjects "resistant" to the *0.30 Gm. dose.*

We have made only a small start in the attack upon this stupendous task by an attempt in the direction of demonstrating the use of a method that might pos-

sibly serve as a means of such study. It is submitted for criticism and, if such a scheme of analysis be found useful, it is hoped that it may be adopted for

Fig. 10. Phenolphthalein 0.60 Gm. Cases.

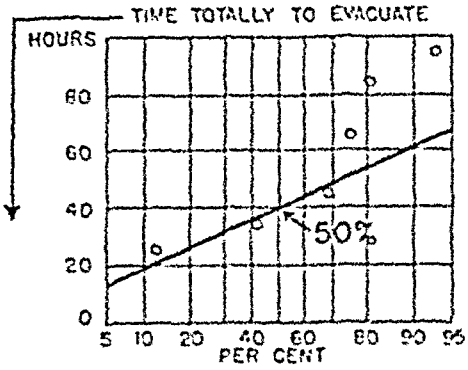


Fig. 10. *Phenolphthalein 0.60 Gm. Cases.* Gut evacuation time incidence plotted as percentages on probability paper. The most probable mean value lies at 40 hours.

cooperative study by possibly many groups of investigators.

THE METHOD

The observations which are here reported were conducted upon male inmates of the Chicago State Hospital for the Insane. Only men were examined who were mildly afflicted mentally, i.e. persons near enough to normal to be more or less fully employed at some useful work about the institution. It was hoped that a proper understanding of the bowel function might be of distinct advantage in the management of these patients. None of the subjects had physical defects that would unfit them for a moderate degree of physical labor. They were admittedly

Fig. 11. Comparison of Gut Evacuation Time in Controls and After 0.60 Gm. of Phenolphthalein.

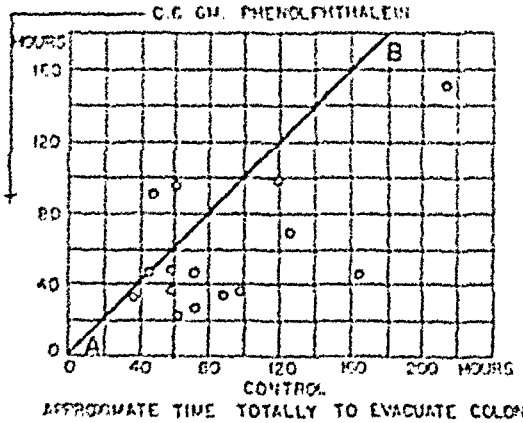


Fig. 11. Comparison of gut evacuation time in controls (abscissae) and after 0.60 Gm. of phenolphthalein (ordinates). While in most individuals the time was shortened, there were two in whom it was increased.

less active than a cross-section of normal healthy individuals. Nevertheless, the bodily activity of the persons studied was quite comparable to that of an ordinary office worker with the proviso that the "mental activity" of these subjects was on a distinctly lower level since at best the tasks which they performed were largely menial and of a routine nature.

It should be specifically noted that all the subjects were offered the same diet which for purposes of comparison is a very important consideration; though, it must be admitted that there was no check on the amount of each constituent or the total quantity actually consumed, a matter also of considerable importance.

The ages of the men ranged from 21 to 68 years with the average about 40. They were chosen at random, with no regard to their bowel function. Several of the subjects did complain of constipation, but no special attention was paid to this matter in the present study as method rather than therapeutically valid deductions was all that could

Fig. 12. Gut Evacuation Time Curves of Individuals Without (0) and With Phenolphthalein.

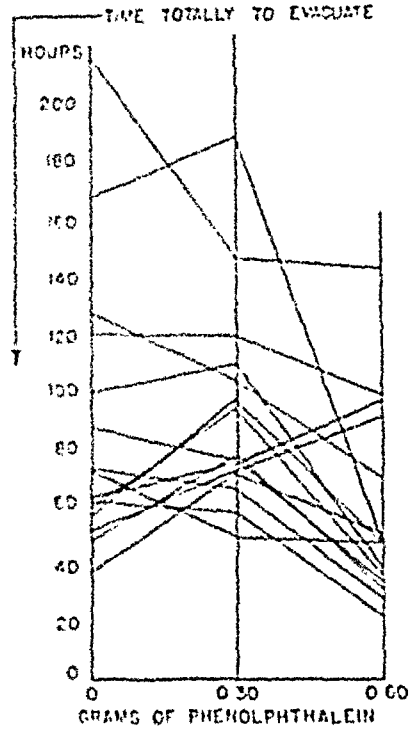


Fig. 12. Gut evacuation time curves in controls (0) and after 0.30 Gm. and 0.60 Gm. of phenolphthalein. Each line represents observations on one individual. Downward slope shows decrease in evacuation time; upward slope, increase in evacuation time.

be aimed at. This fact will also largely answer the objection which may be raised that the results secured from the study upon insane persons cannot be applicable for normal individuals. It may furthermore be emphasized that this study is not invalidated by the fact that it was carried on upon the insane for the following additional reasons:

(1) Controls were secured by taking a gastro-intestinal X-ray series before as well as after the giving of the cathartic.

(2) It will probably be difficult, excepting in prison populations, to find a group of individuals living under more nearly similar conditions of exercise and of diet.

(3) As has previously been stated, individuals physically normal were chosen.

Should subsequent investigation show that we have encountered great deviations from the average of physically similar individuals who are mentally normal, this study might serve as a beginning of the understanding of the intestinal functions of the insane.

Fig. 13. Control Cases.

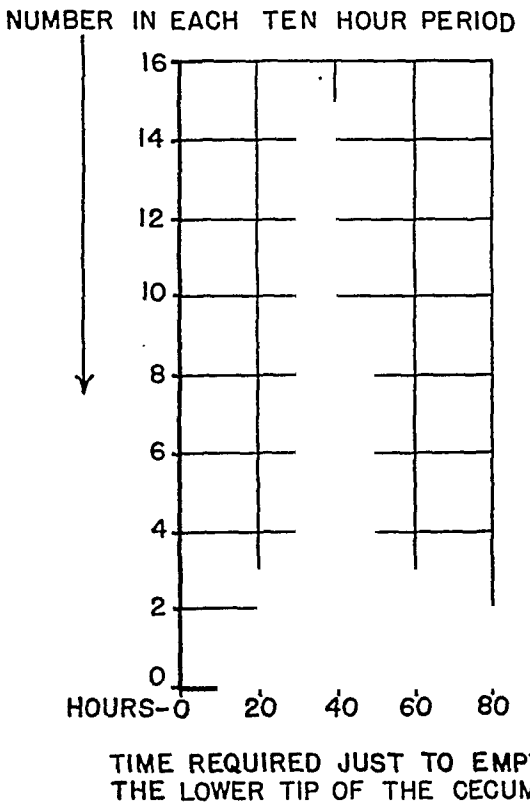


Fig. 13. *Control Cecal Tip Evacuation Time.* Frequency distribution graph.

TEST WITH CATHARTIC (PHENOLPHTHALEIN)

The tests to be reported include 61 control series on 36 individuals, 32 series after the giving of 0.30 Gm. of phenolphthalein to 32 individuals, chosen at random from the 36, and 16 series after the administration of 0.60 Gm. of phenolphthalein to 16 individuals, 15 of whom had been found to be more or less refractory to the 0.30 Gm. dose of phenolphthalein.

The tests were conducted in a uniform manner. They were always begun about one-half hour after the Sunday morning breakfast, the day when the men were least occupied. Each individual ingested 60 grams of barium sulfate suspended in water. When phenolphthalein was given a week or more later, it was mixed with the barium sulfate and the patients were entirely unaware of having received a cathartic and had no knowledge other than that the same examinations were being made each time. The influence of suggestion, therefore, was eliminated as a factor and played absolutely no part in the results.

Three radiographs were made the first day, one and one-half, three, and about ten hours after the ingestion of the opaque material, and then one on each succeeding day at 8:00 a. m. until total evacuation had occurred.

Size 14 x 17 inch pieces of photographically sensitized paper were used for making the radiographs, since the cost of this paper is only about one-half that of the ordinarily used X-ray film. The exposures were all made with the patient lying with the ventral surface down on a Potter-Bucky horizontal radiographic table, giving postero-anterior views of the abdomen and pelvis.

An effort was made to record all bowel movements from two days before the study was begun until at least a day after it was finished, but these data could not be utilized since a large percentage of the statements of the patients was obviously unreliable.

Reproductions of most of the radiographs of a typical test secured on one individual are presented in Figure 1.

The radiographs were carefully scrutinized and tabulations were made as to the times involved in the passage of the opaque meal through various parts of the digestive tract. Other less definite factors that might in any way have a bearing on the problem were also noted. While the radiographs revealed no evidence of the production of a generalized or localized spasticity as usually interpreted roentgenologically, the possibility of colon spasm having been produced is by no means eliminated as but few fluoroscopic examinations were made. The patterns were all of just about the appearance that would be encountered among normal individuals in the routine work of an X-ray laboratory. No types of greatly abnormal appearance were encountered.

The data from each series of radiographs were plotted, making what in reality constitutes a motility diagram of the gastro-intestinal tract under the particular conditions that prevailed during the test. The different regions of the gastro-intestinal tract were represented symbolically by appropriate lengths and the cross-sections by the separation between parallel lines. The parts of a normal adult digestive tract average in lengths as follows:

Stomach	three-fourths of a foot
Small intestine	20 feet
Colon	Five feet

These ratios were not reproduced exactly in the

Fig. 14. Control Cases.

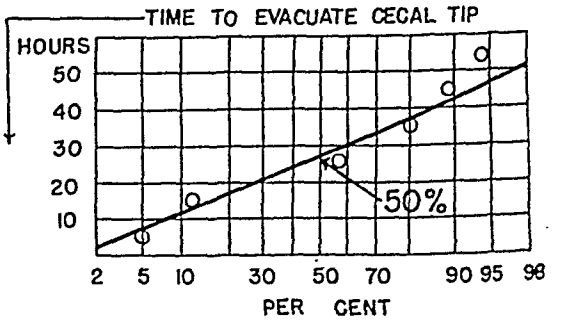


Fig. 14. *Control Cecal Tip Evacuation Time.* Number of cases expressed in percentages plotted on probability paper. Most probable mean value: 27 hours.

schematic diagrams. The abscissa scale represents time and the position of the opaque meal in each radiograph is indicated by shading. Each radiographic examination was shown pictorially by a sepa-

Fig. 15. Phenolphthalein 0.30 Gm. Cases.

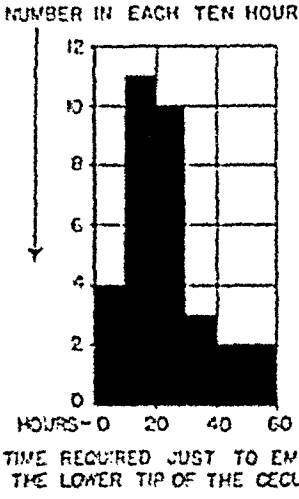


Fig. 15. Phenolphthalein 0.30 Gm. Cases. Cecal tip evacuation time. Frequency distribution graph.

rate sketch of the gut so placed as to indicate the time at which the radiograph was taken. Curves were constructed to show the location of the tail of the column of opaque material at the various times (Fig. 2). It was then possible to secure a direct comparison of these motility curves by superposing them (Fig. 3).

CONTROL STUDIES AS TO TOTAL EVACUATION TIME

Figure 4 shows the frequency distribution of the time required by controls for total evacuation, using the average evacuation time of the two control runs of each of the individuals studied. The summated data for the same group of tests are shown in Figure 5. The same data are shown on Figure 6 when plotted on "probability paper." These data show that the most probable mean time completely to evacuate ingested material is normally 70 hours.

PHENOLPHTHALEIN (0.30 GM.) TOTAL EVACUATION TIME

The frequency distribution of time totally to evacuate the opaque material when 0.30 Gm. of phenolphthalein is ingested is shown in Figure 7. The same data plotted on probability paper (Fig. 8) show that the most probable mean time completely to evacuate when 0.30 Gm. of phenolphthalein is ingested is 62 hours: a speeding up of just over 10%.

PHENOLPHTHALEIN (0.60 GM.) TOTAL EVACUATION TIME

The frequency distribution of time totally to evacuate is shown in Figure 9 for sixteen "resistant" subjects when they ingested 0.60 Gm. of phenolphthalein; and the same data plotted as percentages on probability paper are shown in Figure 10.

No direct comparison between this graph and that of the similar graphs for the other groups can be made since these subjects were selected resistant cases and not chosen at random as were those of the first group. The most probable mean value of the evacuation time for this group under these conditions is 40 hours (Fig. 9 and 10) which is less than two-thirds of the control value of 70 hours.

COMPARISON OF CONTROL AND OF PHENOLPHTHALEIN EVACUATION TIMES

Figure 11 shows the relation between times totally to evacuate. Each point on Figure 11 represents an individual, the abscissa being the time totally to evacuate for the average of two control tests and the ordinates being the time totally to evacuate when 0.60 Gm. of phenolphthalein was ingested. All points excepting two lie below the line A-B which shows that, while in most of the subjects 0.60 Gm. of phenolphthalein did shorten the evacuation time, in the case of two individuals there was an increase in the time required for the tail of the column to pass through the entire colon.

Figure 12 expresses the same facts in the form of curves. These curves would all descend if a purgative response to phenolphthalein were uniformly realized. The curves of the same two individuals, referred to above, have slopes consistently in the opposite direction, even after a 0.60 Gm. dose of phenolphthalein.

"CECAL TIP EVACUATION TIME"

Figure 13 shows the time required for the tail of the column just to leave the lower tip of the cecum in the control observations. This factor seems to hold promise as a quantity for comparative analysis since the values are bunched and a rather well formed curve results. Owing possibly to reverse peristalsis, it seems almost impossible to get consistent results from the use of other criteria.

Figure 14 shows that the most probable value of the cecal tip evacuation time was 27 hours. The same time relations after the ingestion of 0.30 Gm. of phenolphthalein are shown in Figures 15 and 16 which give 18 hours as the most probable value for cecal tip evacua-

Fig. 16. Phenolphthalein 0.30 Gm. Cases.

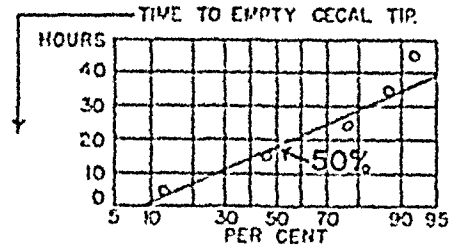


Fig. 16. Phenolphthalein 0.30 Gm. Cases. Cecal tip evacuation time. Number of cases expressed in percentages plotted on probability paper. Most probable mean value: 18 hours.

tion after the ingestion of 0.30 Gm. of phenolphthalein, a speeding up by one-third.

There are fewer individuals whose cecal tip evacuation time is not influenced by phenolphthalein than there are whose total evacuation time is not influenced. This indicates that *the chief evacuant effect of phenolphthalein is probably exerted in the cecum.* It might

also be stated that the total evacuation time in many cases was unduly prolonged by the retention of only a relatively small amount of opaque material of possibly questionable importance.

Detailed investigation of those exceptional individuals whose evacuation time was definitely increased by even 0.60 Gm. dosage of phenolphthalein might furnish valuable hints for the understanding of the mode of action of phenolphthalein and also help in the elaboration of more definite indications and contraindications for the use of phenolphthalein as a cathartic.

RECOMMENDATIONS

As the number of subjects investigated in this study was rather small, studies of a larger series would yield information of greater reliability.

More intelligent subjects would be highly desirable because they would cooperate more fully and give information as to frequency and condition of bowel movement which should be incorporated in data of this type.

Exhaustive studies of resistant subjects might yield very significant data.

CONCLUSIONS

1. A method is described for the graphic representation of the progress of an opaque meal through the alimentary tract and for deriving data of possible use in the evaluation of the motility of human alimentary tracts.

2. In the relatively small group studied, the most probable value of the total evacuation time was 70 hours and of the cecal tip evacuation time just under 27 hours.

3. The most probable time for the opaque meal to be evacuated completely when 0.30 Gm. of phenolphthalein had been ingested was 62 hours: a decrease of over ten per cent; and the cecal tip evacuation time just under 18 hours: a decrease of thirty-three per cent.

4. When subjects, who were "resistant" to 0.30 Gm. of phenolphthalein, ingested 0.60 Gm. of phenolphthalein, the most probable time totally to evacuate was 40 hours, which is significantly below the control time and of the 0.30 Gm. of phenolphthalein evacuation time of the entire group. There were, however, exceptional individuals whose evacuation time was definitely increased by both 0.30 Gm. and 0.60 Gm. doses of phenolphthalein.

5. It seems that the time required totally to evacuate, and possibly also the time required just to empty the lower tip of the cecum, might be useful criteria for judging the action of cathartics.

Host Susceptibility to Common Colds*

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A CAUSATIVE agent of disease in man must enter the body by passing through some surface covering layer, skin or mucous membrane. Some of the agents causing disease gain entrance through abrasions of these surfaces and belong to the wound infecting group. Most of the diseases however are produced by viruses, bacteria and parasites that invade the body by passing through an intact mucosa, the upper respiratory or digestive mucous membrane. The normal defensive power of the body against such invaders resides in the ability of these membranes to prevent the invasion after contact.

Man must adapt himself to his environment in order to maintain health. Environment can be subdivided into various factors, such as: (1) Meteorological or climatic, (2) nutritional, (3) mental and (4) parasitic. This article will present our experimental and clinical observations upon common colds considered from the standpoint of maladjustment to these environmental factors.

The mucosa of the upper respiratory tract is an unusual body surface covering layer. Embryologically it is closely related to the skin. The mucosa of the nose has several physiological functions in addition to those of a limiting integument or covering for this body surface.

Hill and Muecke (1913) showed that the mucosa of the nose becomes "flushed and swells" when a normal subject is placed in a warm moist atmosphere (80° F.). The lumen is narrowed and even choked. When the subject passed to a cold atmosphere the mucosa quickly became pale owing to constriction of the blood vessels, but still remained thickened or swollen. Mudd and Grant (1919), Mudd, Goldman and Grant (1921), Mudd, Grant and Goldman (1921) were the first to study the relationship between the chilling of the skin and the temperature of the mucosa of the nose and throat. Azzi (1920, 1921, 1921) in Italy carried on similar experiments at the same time. Azzi extended the respiratory mucous membrane surface to include the trachea in man. He had the opportunity of using some tracheotomized subjects for this study. Winslow and Greenburg (1932) extended the observations of the vasomotor reactions of the nasal mucous membrane to cold stimuli applied to the skin. Schmidt and Kairies (1932) in Germany and Undritz and Sassosow (1933) in Russia, carried out some extensive work at the same time in this field. The technical methods used by all of these observers were in general the same.

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These workers differed in their procedure of applying the skin stimuli, such as stripping subject and using cold wind current on back, immersing foot or hand in cold water, applying cold, wet towel to back, chest or other body surface.

Townsend (1924) showed that epidemics of common colds occurred from the Pacific to the Atlantic coast at approximately the same time in each locality. Van Leghem (1928) studied the incidence of common colds in Holland and found the same thing. He found that the attack rate in small and large family groups was the same and concluded that "This joint result tells against the contagiousness of colds in the period of observation." Bibb (1924) analyzed the incidence of common colds in a military population and concluded that communicability played a minor role. Many more such observations could be cited. Kerr and Lapen (1931) could not transmit common colds to healthy human volunteers in air conditioned rooms held at "effective temperatures." During the early stages of the disease, common cold sufferers lived with volunteers in this room. The volunteers were inoculated in their conjunctival sac with secretions from the coryza patients' nares.

Several observers have emphasized the influence of meteorological environment upon the incidence of common colds, which presumably has a relationship to external temperature. Selado (1919), Van Leghem (1928) and Bibb (1924) and others have developed the thought that disturbances in the heat regulatory function of man due to climatic changes are the basis for increased susceptibility of the host to common colds.

Smiley (1929) showed that the winter or spring epidemic of cold among college students was mostly limited to the cold-susceptible group. Only one-fourth of the student population was responsible for the increased incidence of cold at these seasons. He concluded that if this group were made resistant to common colds, the winter and spring epidemics would disappear.

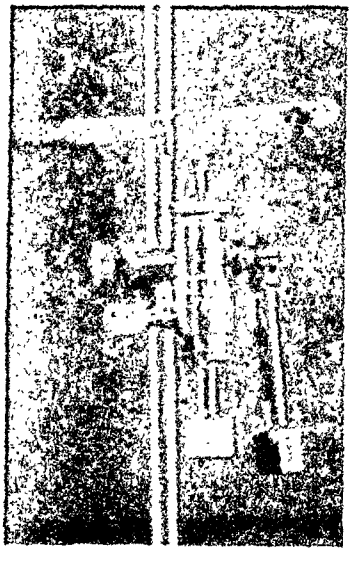


Fig. 1

Galafer (1932) could find no decrease in the incidence of colds when some 300 subjects slept in rooms with open windows and took out-of-door exercise.

For an understanding of the reactions of the respiratory tract to external influences, it is well perhaps

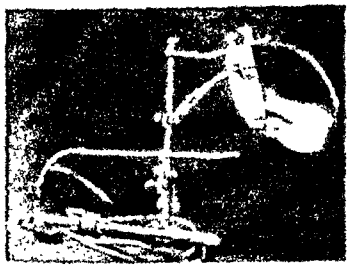


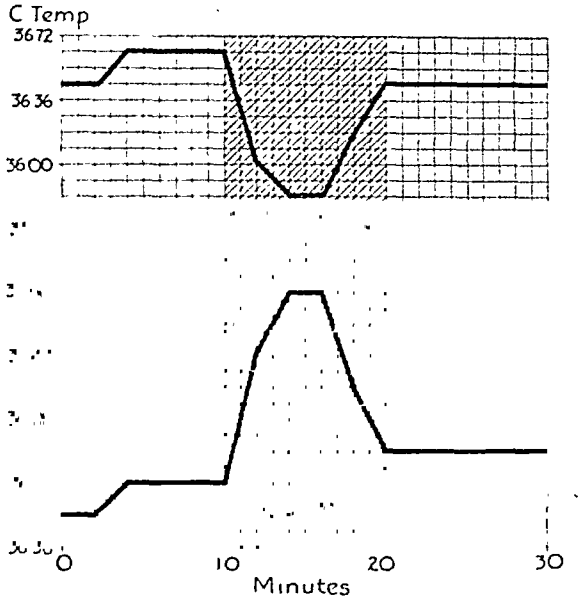
Fig. 2

at this time to review the physiology of the nose. One of the primary functions of the nasal mucous membrane is its ability to supply moisture to the inspired air. This moisture is supplied through the physiologic reactions occurring in the erectile tissue of the turbinates. Closely associated with the process of moistening or humidifying is the heating of the inspired air. This function is accomplished by the large and numerous blood vessel spaces in the deeper layers of the mucous membrane of the turbinates. Another important function of the nose is its ability to filter the inspired air. Coarse particles in the air are filtered out by vibrissae within the vestibule of the nostrils. The turbinates break up the column of inspired air, producing eddies, so that most of the air comes in contact with some part of the surface covering mucous membrane. This facilitates the deposit of foreign particles on membrane. Wright and Smith (1914) state that thin sheets of air in passing over these surfaces deposit at least three-fourths of their bacterial content on the mucosa. The dust and foreign particles including bacteria thus deposited on the mucous membrane are disposed of, in part at least, by the action of cilia with the protective layer of mucus. Goodale (1895) was the first to show that air taken in through the nose and exhaled from the mouth gave the greatest increase in temperature and relative humidity. He also demonstrated that while the nose nearly saturates the air, it contributes only about two-thirds of the total amount of moisture evaporated by the respiratory tract.

The vasomotor mechanism of the nose involves the physiologic activity of two sets of antagonistic sympathetic nerves, the vasoconstrictors and the vasodilators. The constrictor fibres consist of preganglionic fibres arising from the central nervous system and postganglionic fibres from the cells of the sympathetic ganglions. The vasoconstrictor fibres arise chiefly from the cervical sympathetic ganglia. The vasodilators are not as powerful as the vasoconstrictors. Not much is known regarding the vasodilator fibres. They arise from the cervical sympathetic and from the ganglia and connecting sympathetic of the seventh and ninth cervical nerves.

Hilding (1931, 1932, 1932, 1932) states that the film of secretion covering the membrane of the respiratory tract extends like a continuous membrane over the surface of the nose, the paranasal sinuses,

pharynx and the trachea. This film of mucus is in continuous motion throughout this entire extent of surface. The general direction of flow is toward the nasopharynx. The mucinous covering is kept in motion by direct ciliary activity. Lucas and Douglas (1934) showed that the mucous sheet which covers the cilia is composed of two layers, an outer stratum of mucus which rests on the top of the cilia and an inner fluid layer of low visocosity which forms a suitable medium for the vibrating cilia. They emphasized the possible importance of the fluid layer as a mechanism of dissemination of bacteria and viruses. Phillips (1926) and Gordonoff and Mauderli (1936) showed that ciliary action was sluggish and delayed after an acute



Common Cold Resistant Type

Graph III. Upper line represents nasal mucosa temperature changing after cold stimulus is applied to skin of back. Lower line represents the same after application of heat.

upper respiratory infection, and that healthy ciliated epithelium is a most important factor in maintaining a normal sinus condition.

That filtration, humidification, temperature regulation of the inspired air play an important part in the protection of the nose. (Heetderks, 1927) paranasal sinuses and the lower respiratory tract against deleterious influences is now accepted without question. Ciliary action and mucous secretion also play an important part in the protection of the underlying mucosa against the deleterious effects of foreign agents, especially bacteria. The vibrissae of the nasal vestibule play some part in filtering out gross particles from the inspired air which under ordinary conditions contains few pathogenic organisms. It has long been suspected that some antibacterial substance in the secretions is a contributing factor. Hilding (1930) points out that the protective coat of mucus and ciliary activity are important factors in removing bacteria from the nose and sinuses. Fleming (1929) found lysozyme present in a large number of tissues and secretions from the human body. Considerable quantities were found in nasal sinuses and in saliva. The properties of lysozyme have been studied by Ridley (1927) who concluded that the action of lysozyme on bacteria causes them to swell, lose their outlines and disappear.

Kisskalt (1903) and some of his students (Maugeri (1933), Krishnamurthy (1935) and Margaritis (1936)) have studied the fate of bacteria in the respiratory tract in animals. They ascribe a phagocytic function to the epithelial cells. Ropes (1929) found the ciliated cells in the trachea and bronchii of rabbits phagocytized carbon particles. This function may play a role in the upper part of this tract and may be a factor in defense against bacterial invasion.

The whole problem of resistance of the mucosa of the upper respiratory tract to infection has been recently reviewed in considerable detail by Linton (1933).

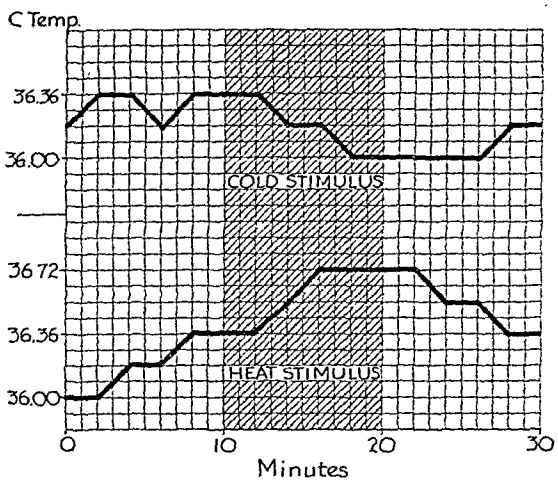
The susceptibility to the common cold has been approached from numerous angles. Dietary inadequacies, particularly of vitamins, have been suspected as being in the background of susceptibility. Numerous investigations have concerned themselves with the specific immunity of the individual to bacterial antigens; a number have dealt with the role of vasomotor phenomena in susceptibility to upper respiratory infection. Spiesman (1935, 1936) reported his observations upon the vasomotor response of the nasal mucosa to thermal stimuli applied to various areas of the skin. These reports dealt more with the physiology of the mechanism of the relationship of skin stimuli and nasal mucosal capillary response. The previous reports dealt largely with the situation in normal individuals and only brief reference was made to the findings in subjects with head colds. The primary object of this investigation was to provide a means of study of altered function in the subjects with head colds.

Thirty-nine patients were included in this investigation, excluding the twenty-four normal subjects whose findings have already been reported. In the 39 cases "colds" of various variety were studied. Thirty-four of this number were adults, five were children; twenty-three were males and sixteen females; the age distribution of this group varied from six to fifty-four years. Twenty-one of this group were classified as the chronic cold group because these subjects had had more than three colds a year, as distinguished from the already mentioned twenty-four cases, or cold resistant group which had not more than one "cold" per year.

All of the thirty-nine cases were selected from the outdoor clinic patients applying for relief after having had a long history of various types of treatment previously received but who nevertheless came to the clinic presumably because their symptoms continued in spite of previous treatment. A complete history was taken on each patient and a general physical examination made including X-ray of the sinuses and chest. The patients finally chosen for this study presented no detectable pathology as determined by the above methods of examination. It was advisable to eliminate those who suffered from repeated head colds and who showed sinus pathology since an infected or inflammed sinus would in itself predispose the patient to repeated infections.

The vasomotor reflex mechanisms were investigated by the following method. A three element thermopile made of No. 30 German silver wire and No. 25 copper

wire mounted in a Bakelite block, as indicated in Figure 1, was placed lightly on the mucosa of the inferior turbinate. The pressure was adjusted with a micrometer screw arrangement attached to the headgear as shown in Figure 2. The constant temperature



Chronic Infectious Common Cold Type

Graph IV. Upper line represents nasal mucosa temperature changing after cold stimulus is applied to skin of back. Lower line represents the same after application of heat.

junctions of the thermocouple were placed in the thermos jar filled with chipped ice. A type K potentiometer and a sensitive galvanometer were used to measure the voltage differences corresponding to the temperature differences in the two thermocouples. In the system as used 2 x 10-5 power volts equals 0.018° C.

APPEARANCE OF NASAL MUCOSA

The appearance of the nasal mucosa of the young healthy subjects studied was pinkish in color. When a cold stimulus was applied to the skin over a small portion of the upper back no noticeable change in the appearance of the nasal mucosa was seen. Changes in appearance of nasal mucosa (ischemia) were definitely seen when larger skin areas were stimulated, as for instance, when applying cold water to the skin of the entire back or immersing the lower limbs in cold water. The presence of ischemia was dependent on the amount of skin area stimulated.

SITE OF THE NASAL ELECTRODE

At first the nasal thermopile electrode was applied to various areas of the nasal mucosa to determine which area was most practical for our experiments. The following areas were studied; inferior turbinate, middle meatus, middle turbinate, superior meatus, and septum. Except for the septum, the results were alike in all the areas mentioned. However, for all practical purposes, we found that the anterior half of the inferior turbinate was most accessible because in this area the electrode could be applied without causing any irritation to the surrounding mucosa. When applying the electrode to the nasal mucosa great care had to be exercised, since any irritation of the mucosa created by the electrode produced congestion with increased temperature and excess mucous formation.

The electrode after being applied to the nasal mucosa was held in place by an adjustable clamp attached to a head gear. The nasal clamp had a micrometer adjustment for making desired pressure upon the electrode tip on the mucosa. By previous experiments we found that too light pressure allowed the respiratory air to circulate around the tip of the electrode thereby preventing correct temperature measurements. Very firm pressure of the electrode to the nasal mucosa brought about local irritation. Moderate pressure gave the desired results, however, and the micrometer adjustment made possible the application of the desired pressure to the mucosa.

PREPARATION OF THE SUBJECT

The subject was brought into the experimental laboratory; a room about 8 feet square in which the temperature did not vary and drafts were minimized. He stripped to the waist and remained at ease in sitting posture until the experiment was begun. A record was made of the condition of his nasal mucosa before the experiments. At the end of the half hour, the electrode was applied and the control temperature record was made of the nasal mucosa, a reading every 2 minutes for five readings. The experimental subject arrived at the laboratory usually one hour after breakfast. Readings were made five mornings each week: Monday, Tuesday, Thursday, Friday and Saturday. The same subject was studied weekly from four to six months during the winter. Several subjects remained for study throughout the summer and weekly records were made of their nasal mucous membrane temperatures. The experiments were all conducted before noon, usually between 9:00 and 12:00. The skin area stimulated by choice was that of the upper back; the duration of the experiment was thirty minutes, as follows: ten minutes for control temperature, ten minutes to record changes due to application of the cold stimulus followed by another ten minutes for a control record.

Each subject was studied as described above for a period of three to five weeks to determine the average nasal mucosal response to a cold stimulus applied to the skin of the upper back. Various treatments were then prescribed and observations continued at weekly intervals for several months.

Spiesman (1936) has outlined in detail various methods of applying thermal stimuli to skin surfaces while recording the temperature changes of the nasal mucosa. The reports we are including in this paper were made with the use of a uniform technic as follows:

Aluminum cups, varying in diameter from four to nineteen centimeters filled with chipped ice were used as cold stimuli. The ice-filled cups gave a surface skin temperature of 12.6° C. within a minute. Aluminum cups filled with hot water were used as heat stimuli. The hot water ranged from 42.5 to 43.5° C. The subject's back was bare of clothing when the thermal stimulus was applied. There was a ten minutes' period of observation before the thermal stimulus was put on the skin. This was to obtain a normal curve of the temperature and to record the influence of the local irritating factor of the electrode applied to the nasal mucosa.

Graph III illustrates the average of several hundred observations made on normal subjects. The upper line records the temperature of the nasal mucosa for thirty minutes period of time. The first ten minutes is the control period, the next or middle ten minutes is the duration of the time the cold stimulus was applied to the skin of the back. The last ten minutes period records the temperature of the nasal mucosa after the cold stimulus was removed from the back.

Attention should be called to the prompt lowering of the temperature of the nasal mucosa immediately after the cold stimulus is applied to the skin and the gradual recovery or return to approximate normal temperature level even while the stimulus is still being applied. Recovery of the nasal vasomotor reaction is complete during the ten minutes time of ap-

plication. There is no change in the temperature of the nasal mucosa after this equilibrium is reached. This is characteristic of the normal person.

The lower line on Graph III records the temperature changes of the nasal mucosa as a result of applying a hot stimulus to the skin of the back. This is characteristic of the normal person. The same general statements can be made for this warm stimulus as have been made for the cold stimulus.

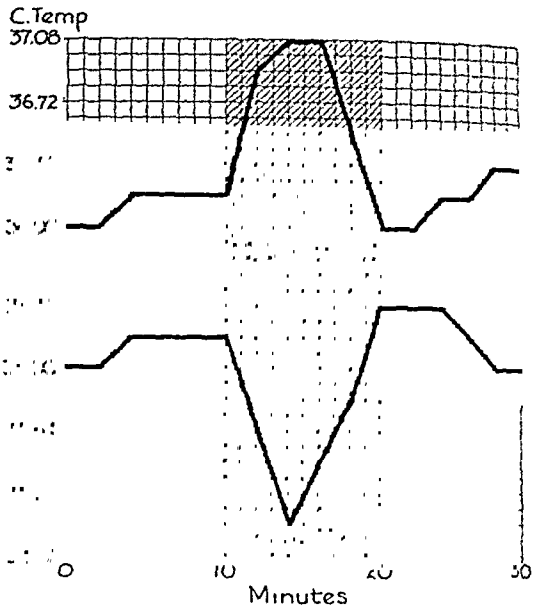
THE CHRONIC OR FREQUENT COMMON COLD SUFFERER

Graph IV records the temperature changes of the mucosa of the nose before, during and after application of thermal stimuli to the skin of the back. The control or the ten minutes period before application of the stimulus shows deviations from the normal. The initial temperature is usually lower, and the mechanical stimulus of the electrode gives variable responses. The nasal mucosal response to cold skin stimuli is delayed and never varies greatly in magnitude. Recovery is delayed and extends for fifteen to twenty minutes or more in time as compared to prompt and quick recovery of vasomotor equilibrium in the normal (Graph III). There are considerable variations in the response of different subjects and even in the same subject on different days. The pattern of vasomotor response of the nasal mucosa to cold and hot stimuli applied to the skin is regular in the normal individual, but manifests considerable variations in the chronic, repeated or frequent sufferer from common colds. These experiments were carried out on these subjects at the times they were free of colds or between their attacks.

THE HYPERSENSITIVE CASES

At first all of our cases were received as patients with frequent head colds. After studying these persons we immediately had on hand two classes of patients: (1), the chronic group of head colds, and (2), the non-infectious or hypersensitive group. This latter group was classed as hypersensitive because the subjects presented a syndrome, during an attack, which was characterized by sneezing, itching, nasal obstruction, nasal discharge and loss of the sense of smell associated mostly with a pale discoloration of the nasal mucous membrane. Anyone or more of these symptoms dominated the clinical picture. The frequency, duration and degree of these symptoms varied a great deal in individual cases. Although all of this group was given skin tests to determine the particular sensitivity, their skin reactions to various allergens was negative. It is generally admitted that from the standpoint of symptoms as described above that these cases of hypersensitive rhinitis are of allergic origin in spite of negative skin tests and that in these particular cases the nasal mucous membrane is hypersensitive, although the skin tests were negative.

Graph V illustrates the average temperature response of the nasal mucosa of the hypersensitive or allergic group to thermal stimuli applied to the skin of the upper back. The control or the ten minutes' period of temperature observation does not deviate from the normal person. The vasomotor response of the nasal mucosa is just the opposite to that of the normal; an increased temperature when cold stimulus is applied to the skin and a decreased nasal mucosal temperature when heat is applied to the skin. This has held true for all of the subjects in this group. The recovery period after removal of the thermal stimuli is not as uniform as in normal subjects. It requires a longer period of time before an equilibrium is



Allergic or Hypersensitive Cold Type

Graph V. Upper line represents nasal mucosa temperature changing after cold stimulus is applied to skin of back. Lower line represents the same after application of heat.

reached. The general pattern of this curve as shown in Graph V is typical for this group of subjects.

We have been able to classify the subjects we have studied into three groups:

(1) The normal or the individual who rarely has a common cold. (Graph III).

(2) The chronic or frequent common cold sufferer. (Graph IV).

(3) The hypersensitive or allergic type. (Graph V).

It became very apparent to us in the early part of this work that if one wished to apply any preventive methods it would be necessary to differentiate between these three groups. Preventive procedures applied to the normal group would not alter the usual physiological vasomotor response of the nasal mucosa to thermal stimuli applied to the skin.

Autogenous vaccines were administered to eighteen patients of the chronic common cold group. The vaccines were prepared from organisms cultured from the respiratory and digestive tracts, following only part of the suggestion made by Dorst and Morris (1930) to include intestinal strains. Sensitization tests were not made, however, in this group. The following bacteria were isolated in pure culture and vaccines prepared from each in the usual manner.

Respiratory Tract:

Streptococcus viridans and micrococcus catarrhalis. Streptococcus hemolyticus. Staphylococcus albus. Staphylococcus aureus. Staphylococcus hemolyticus.

Digestive Tract:

Streptococcus viridans (most frequently found and in the same strains as in the respiratory tract). Bacillus coli communis. Bacillus coli communior. Bacillus coli hemolyticus. Bacillus mucosus capsulatus. Bacillus fecalis alkaligines. Bacillus acidi lactici. Bacillus proteus. Bacillus cloacae.

From two to six bacterial antigens were included in a polyvalent vaccine. Injections were given subcutaneously every other day, beginning with one minim dose and increasing slowly to produce the local or focal reactions; maximal dose was one c.c. The total treatment lasted three months. The frequency of colds was not affected by this treatment, nor was there any effect produced upon the vasomotor responses of the subject in question. We devoted a year to the vaccine studies. Our results using the nasal vasomotor reflex and clinical observations coincide with the negative findings reported by Sholly and Park (1921), Ferguson, Davey and Topley (1927), Brown (1932), Dochez (1933), Hoyle (1933), Kneeland (1934) and many others, all of whom were unable to show any protection against colds after the use of vaccines.

Spiesman (1936) showed that if the skin was anesthetized the application of the thermal stimuli still produced the same vasomotor response in the nasal mucosa, pain was therefore not the factor in this mechanism. Lowered temperature was due to vasoconstriction and an elevation in temperature was caused by vasodilatation. In other words, pain was not a factor in this vasomotor reflex response.

It was, therefore, concluded to attempt to increase the efficiency of the vasomotor tonus mechanism of the nasal mucosa of the chronic cold and the hypersensitive types by hydrotherapy. These subjects were not hospitalized; our object was to apply simple methods applicable by anyone desiring to carry them out. Each subject received instructions to take a hot bath and cool or cold shower on arising each morning and repeat if possible each evening before dinner. The water was to be warm enough to be comfortable; followed immediately with cold water, applied first to the legs, thighs, abdomen, chest and then the back. The cold water was not to be applied to the extent of chilling the body. If the patient became chilled, which was frequent at first for the hypersensitive group, a warm shower should be taken immediately. Once each week a temperature reading was made of the nasal mucosa applying both heat and cold to the back.

The same hydrotherapy was carried out on the hypersensitive group. There was little improvement in the nasal vasomotor tonus, in many of these subjects. This group requires long study because of their unstable reactions before one can arrive at trustworthy end points. It was apparent that some few were markedly improved, but most of them showed little benefit, either in vasomotor response or clinically in a reduction in the incidence of their colds.

After six weeks of hydrotherapy, the hypersensitive group was placed upon an elimination or non-allergic diet as outlined by Rowe (1931). For the purpose of completion we are listing the diet used at this place:

Cereals — Rice, Corn, Tapioca; *Meats* — Lamb, Chicken, Bacon; *Vegetables* — Lettuce, Spinach, Carrot, Squash, Asparagus, Pea, Artichoke; *Fruits* — Lemon, Pear, Peach, Pineapple, Apricot, Prune; *Also* — Sugar, Karo Syrup, Maple Syrup, Mazola Oil, Olive Oil, Olives, Salt.

After the six weeks, if the patient showed sufficient improvement the following foods were added: beef, tomato, beet, string-bean, celery, grapefruit, Wesson oil. The hypersensitive group showed greater improvement on the combined non-allergic diet and the hydrotherapy than on hydrotherapy alone. During the three years, while these patients were under observation, the hypersensitive group was placed on the elimination diet alone, then on vasomotor massage (hydrotherapy) alone for a period of three months. The best results were obtained with the combined treatment of diet and vasomotor massage. A larger number returned to the normal vasomotor response and were free of upper respiratory disturbances. However, this group proved its vasomotor instability over and again by reverting to type after experiencing mental maladjustment. Apprehension and worry produced a complete recurrence of symptoms, and alterations in vasomotor responses. While in this state of apprehension, the same treatment produced no effect. All signs of recovery were removed until worry ceased to exist in the patient.

The non-allergic or elimination diet proved so advantageous a factor in assisting the hypersensitive type to gain a better vasomotor response of their nasal mucosa to thermal stimuli applied to the skin, as well as a better feeling of well being and freedom from colds, we thought a modification of this diet might help the chronic cold subject who had not gained vasomotor control by hydrotherapy alone. We had observed during our experience with the hypersensitive group that the ingestion of wheat and wheat products combined with a high carbohydrate content, were most likely to alter the nasal mucosal responses, as well as being associated with the onset of a cold.

Again for the purpose of making a complete and practical record of our experiences we give the diet we have used for this chronic common cold group:

Cereals — Rice, Corn, Rye; *Vegetables* — Lettuce, Tomato, Carrot, Spinach, Squash, Asparagus, Peas, Beet, Stringbean, Celery; *Meats* — Lamb, Chicken, Bacon; *Fruits* — Orange, Grapefruit, Lemon, Apple, Pear, Peach, Pineapple, Prune, Apricot, Plum; *Dairy Products* — Butter (much), Cream, Milk, Cottage Cheese, Egg Yolk; *Also* — Sugar (sparingly), Karo Syrup, Maple Syrup, Mazola Oil, Olive Oil, Olives, Salt.

All products made from wheat, i.e. white flour breads, pastries, pies, cookies, etc., were eliminated from the diet. The patients in this group were requested to abstain from the use of tea, coffee or alcoholic beverages, and to smoke sparingly. They were instructed to eat two large vegetable portions, or a vegetable and fruit salad each day, and to make the salad the main course of the meal. They were also asked to eat as much fresh fruit as they could daily—six ounces of orange juice and six ounces of tomato juice per adult per day. Eight glasses of water were prescribed a day. Fried foods were prohibited. No condiments. Butter was to be added very freely to all cooked vegetables and eaten generally very freely; two to four egg yolks for each adult and one to two for a child per day. The patient was not to hurry while eating, nor be tired or worried. He was to take a short rest after every meal. The day's menu for a patient of the chronic infectious group read:

Breakfast: A glassful of orange juice (adult). One or two additional fruits, fresh or cooked (sugared

sparingly), in good quantity. Cooked cereal of rice or corn meal with milk or cream in moderate portion, or Bacon with buttered toast made from rye, corn or rice flour. Glass of milk if desired.

Lunch: A large portion of vegetable or vegetable and fruit salad. Bread made of special cereal, rice, rye and corn meal with much butter. Milk. Cottage cheese, if desired. Fruit, good portion. Water.

Dinner: Large vegetable salad. Meat, small portion. Two cooked vegetables (non-starchy.) Fruit. One glass of milk. Water.

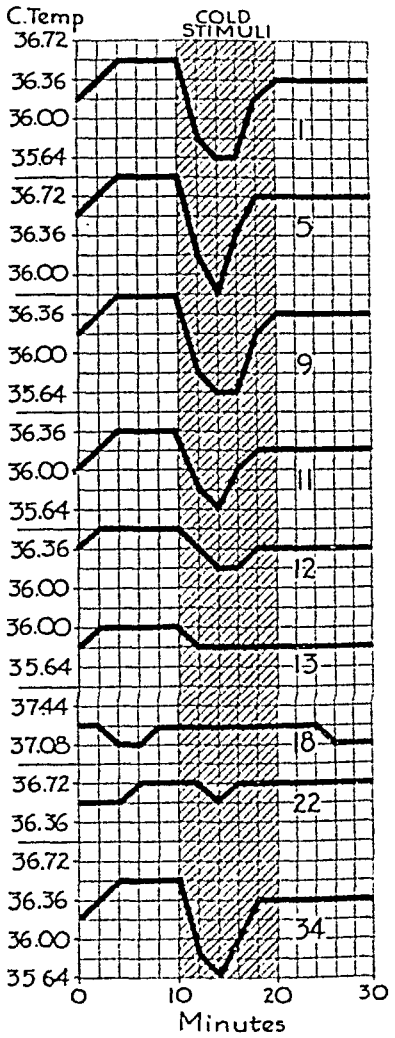
The patients on this regime improved clinically and also in their vasomotor response. During the three year period, the group placed on the diet alone improved much better than on hydrotherapy alone, but best of all on the combined treatment of diet and hydrotherapy. We found, in our experience with dieting of these patients, that an overindulgence of carbohydrates, especially of the wheat-cereal variety, was most to be guarded against. Time and again we observed, after excellent results were obtained, that a return of the patient to an excess carbohydrate diet caused a recurrence of symptoms.

The increased vitamin content, the larger amount of roughage, and other factors are apparent in this diet. These do not, however, explain to our satisfaction the results we obtained. We are now studying this problem. Paton (1933) calls attention to the high ingestion of carbohydrates and the incidence of "catarrhal illnesses." Orr and Gilks (1931) also incriminate a high cereal diet as a factor in mortality from respiratory diseases in their studies of some East African tribes.

After the combined treatment of diet and hydrotherapy the results in both the infectious and non-infectious cases were very satisfactory. However, in some instances, even after careful treatment of diet and hydrotherapy, in both of these groups, individual patients did not produce satisfactory results. That is, the patient under the combined treatment, who had been in good health for some time and free from head colds, infectious or non-infectious, would have, for apparently no reason, a complete relapse with recurrent symptoms and altered vasomotor response. This relapsed state occurred more frequently in the hypersensitive group. Careful observation was then made of these patients and it was found that apprehension and worry were real factors in their condition. Apprehension and worry produced a complete recurrence of symptoms — head colds, and alterations in vasomotor responses. While in this state of apprehension, the same treatment produced no effect. All signs of recovery were absent until worry ceased to exist in the patient.

That apprehension and worry, and unusual emotional activity can produce irregular vasomotor reactions was observed in normals and reported in a previous paper, Spiesman (1936). In hypersensitive cases, where a very irritable and easily altered vasomotor mechanism already exists, continuous good results from the therapy outlined above, is in our experience, maintainable only if the patient's mental attitude is not allowed to change by severe worry or unusual emotional stress. Re-education along the line of mental hygiene is needed therapy for such patients.

One of the normal subjects studied five times per week for several consecutive months in order to determine the daily variations of the nasal vasomotor response, developed a cold during the period of observation. This subject was a healthy young adult male. He had not had a cold for two years. Graph VI shows a few of some eighty-five observations we have made upon this subject. Curve 1, 5 and 9 show

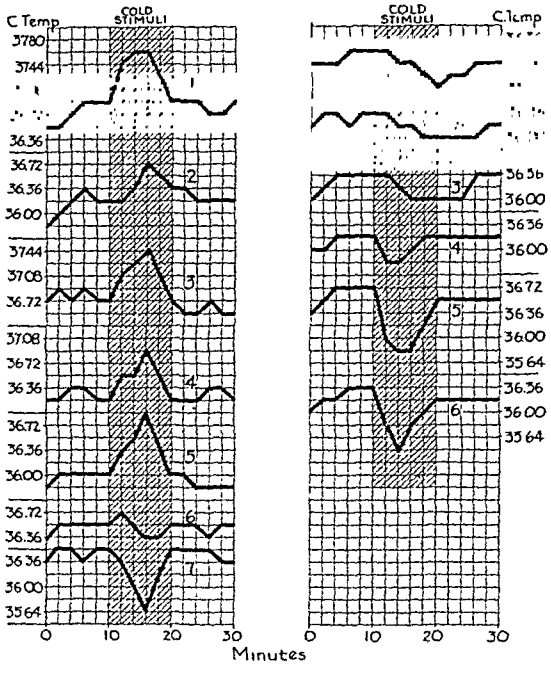


Common Cold Resistant Type

Graph VI. Followed through an attack of acute common cold. Lines 1—11 are normal responses of nasal mucosa temperature to cold stimulus applied to the back. Line 12 represents the incubation period. Lines 13—22 are during the attack of common cold. Line 34 represents the return to normal nasal mucosal response.

averages of the nasal mucosal temperatures observed before, during and after application of cold stimulus to the skin of the back. The last curve (9) was made on a Saturday morning. This subject visited his married sister in her home Sunday afternoon and evening. Two adults and two children in this home were suffering from common colds at the time of his visit.

Curve 11 was made Monday morning; the subject did not complain but felt tired and spoke of having eaten and smoked too much the day before. Curve 12 was his nasal temperature response on Tuesday morning. He complained of headache, backache, etc., but con-



Hypersensitive Type — Chronic Infectious Common Cold Type

Graph VII. Each line represents an average of weekly readings of nasal mucosa response to cold stimulus applied to the back. A gradual return to the normal is shown as a result of hydrotherapy, corrective diet and mental hygiene.

junctiva and nasal mucosa were not altered in general appearance. There was, however, a loss of vasomotor tonus of the nasal mucosa. The next day, Wednesday, (Curve 13) the patient had a typical acute coryza, a conjunctiva injected, continuous aqueous nasal discharge, etc. This subject was then hospitalized. We wished to study his vasomotor reactions daily and did not desire him to be exposed during transit to and from the laboratory. A few of the nasal temperature records are shown on Graph VI. Curves 13, 18 and 22 represent the number of days in consecutive order. Ten days (Curve 22) after the beginning of the infection (Curve 12) the nasal discharge had disappeared. It was, however, twelve days later (Curve 34) before the normal vasomotor tonus returned. Daily observations were made. This illustrates the alterations in the vasomotor tonus of the nasal mucosa of a healthy, cold-resistant person, who has been subjected to a massive exposure of the virus or causative agent and was followed from the incubation through the disease until recovery.

Graph VII represents a few of the nasal temperature records made upon two cases, one a hypersensitive type, the other a chronic or frequent head cold subject. The hydrotherapy, diet and mental hygiene outlined above were carried out by these subjects. The curves are typical averages of weekly readings of nasal temperature after cold stimulus was applied to the back. The hypersensitive case did not show improvement with the sixth week of observation, but after the seventh week he had a normal nasal vasomotor response which has been maintained for over two years. This patient has been checked-up with nasal temperature tests each week during this time.

The other series of curves on Graph VII is from a chronic cold type. It required four weeks after beginning hydrotherapy, combined with certain dietary restrictions and mental hygiene, before this person showed an altered nasal temperature response to a cold skin stimulus. After the fifth week he had a normal nasal vasomotor reaction. This subject has been under observation three and a half years. He has been free of colds during this time.

The mental factor in this readjustment of the nasal vasomotor response cannot be overemphasized. We have frequently and repeatedly observed subjects as indicated in Graph VII change from the normal response, as indicated in the lower curves, back to the abnormal response as shown at the top of each series of curves, as a result of mental maladjustment. Many specific instances could be cited; loss of position, bankruptcy, illness or death of a relative; in fact worry and mental strain of various kinds; all tend to offset the advantages derived from hydrotherapy and diet.

The best preventive measures, as well as the most lasting therapy, for these two groups may be summarized as follows:

1. Vasomotor massage or hydrotherapy given continuously, with the patient made to feel that this is an essential health measure and important to a state of well-being.
2. Diet prescribed not merely as a therapeutic measure, but as a daily measure of intelligent eating for a better state of health.
3. Change of mental state through mental hygiene with the express purpose of producing a more wholesome attitude of the patient to himself and his environment.
4. Physical exercise as an important adjunct of the daily regime. Twenty minutes of setting up exercises, in the nude in a cool room, prior to taking a hot and cold shower. A brisk walk for one hour a day, either in divided time or for the whole hour, walking, never hurrying, breathing deeply and thinking soundly.
5. Rest, even if only for a short period after each meal.

DISCUSSION

The individual suffering from repeated colds between October and April has an altered vasomotor reaction of the upper respiratory mucosa to thermal stimuli applied to the skin. When the skin is chilled, there is a slow, gradual vasoconstriction of the capillaries in the mucosa of the upper respiratory tract which persists for several minutes to two hours. This represents a maladjustment of the peripheral capillary response to climatic or meteorological environment. So long as this abnormal reaction exists the host is susceptible to the common cold virus and the bacterial flora residing in his upper respiratory tract. Such a person becomes a reservoir for the causative agent. We could not alter the vasomotor

response nor reduce the incidence of common colds in this group by vaccine therapy. We have been able to do both by hydrotherapy and certain simple alterations in the diet. The best results were obtained by a combination of both methods of prevention. The mental factor also plays a role, but not to the same extent as was found in the hypersensitive group. We have records showing a normal nasal vasomotor response to thermal stimuli of the skin and a freedom from colds for two years in subjects giving a history of four to six colds each winter for several years. Some few of these subjects due to various reasons, such as loss of their positions, bankruptcy of their business, sudden death of a member of the family, etc., promptly developed a head cold. In two or three instances we were able to demonstrate a change in the vasomotor response of the nasal mucosa for several days preceding the onset of the cold. The mental factor in adaptation of the vasomotor equilibrium of the upper respiratory tract cannot be overemphasized in those persons showing abnormalities in their capillary controlling mechanism.

The hypersensitive or allergic type of cold is more difficult to control and to prevent than the chronic, frequent and severe head cold type. But we have been unable in our experience to trace secondary head colds from anyone of these hypersensitive types. Office, factory, laboratory or class-room contacts closely associated with this type of cold subject have never developed colds. We have, at least up to the present, no evidence that these allergic vasomotor nasal reactions are associated with the infective virus of common colds. Although many interesting problems are presented as a result of our study of these hypersensitive cases, we feel they are not a reservoir for the common head cold virus and their control hence becomes less urgent than that of the chronic infectious head cold group.

The nutritional factor in susceptibility to common colds has been frequently observed by us during this study. It seems that the mucosa of the nose is more sensitive to allergens ingested by mouth than the skin. All of our subjects were studied in the Allergy Clinic and only those showing negative skin tests to various antigens were studied by us. The non-allergic diet helped the hypersensitive group to readjust its vasomotor responses. We have no explanation to offer for the beneficial results obtained in the frequent infectious head cold group following the elimination of wheat breads, pastries, pies, cookies and such rich carbohydrate foods. Our experience convinces us that these foods increase the susceptibility of the chronic cold sufferer to repeated attacks and exercises a detrimental influence upon the nasal vasomotor response to thermal skin stimuli.

The reservoir for the causative agent of common colds is, in the main, confined to the chronic, frequent and repeated head cold subjects. The restriction of the distribution of this virus can best be approached by increasing the resistance of these people to autoinfection. Minor alterations in their environment, meteorological, nutritional or mental, causes a common cold. We have found this group responds to preventive and hygienic procedures better than the hypersensitive group. The hypersensitive type of upper respiratory disturbance is not communicable and from a public health standpoint is not a source of contagious material. We have observed common colds of the infectious type in some of the hypersensitive group, but the clinical picture is different, the nasal discharge and course of the disease are the same as in the other groups.

The hypersensitive type of long standing develops pathology of the mucosa and tends to develop or superimpose upon these altered tissues a chronic infectious cold type. These subjects then become chronic carriers and are therefore a combination of the allergic and chronic infectious type of cold. As stated before, we eliminated these pathological cases before we began our observations.

Massive exposure of the normal resistant person to the causative agent can be followed by infection. The resistance enjoyed, by proper adaptation to the environmental factors discussed, is only relative. The parasitic environment is most important to this resistant type, in as much as these subjects are adjusted to their meterological, nutritional and mental environmental factors.

The repeated or chronic common cold type is out of adjustment to his or her environmental factors and hence requires some corrective measures to assist in adaptation, such as vasomotor stimulation (hydrotherapy), certain dietary restrictions, better mental hygienic control, etc. While in a state of maladjustment this portion of the population acts as reservoirs for the cold virus. Smiley (1929) called attention to this when he stated that less than a fourth of the population, who are the chronic type, are responsible for the winter or spring epidemics.

There are many reports in literature of transmission of common colds by nasal instillation. The results of these experiments vary widely, from success to complete failure. It may well be that the results were to some extent dependent upon the susceptibility of the volunteers used for the experiment. The recent work by Dochez (1936) who has used cultures of the virus may be due to the massive dosage of the virus. The choice of volunteers based upon their vasomotor reflex reactions might lead to newer knowledge upon susceptibility.

We have studied sixty-three subjects over a period of three years. There were some two hundred and fifty subjects examined and observed for varying periods of time, but only sixty-three were under continuous observation. These can be divided into three groups:

1. The resistant or normal type.
2. The chronic, frequent and infectious type.
3. The hypersensitive, non-infectious type.

Vaccines, vitamins, drugs and any other specific prophylactic measure for preventing colds should take into consideration these three groupings of the population. The results obtained in the resistant or normal group will be good for any preventive measure that is physiological and hygienic. Specific prophylactic procedures should be tried on the chronic infectious common cold types.

The extent or magnitude of the maladjustment of chronic or frequent cold sufferers differs in individual cases. Some will find that retaining the vasomotor reflex response by hydrotherapy will be sufficient to prevent colds. Some will find the nutritional factor most important. Others will find the mental factor to be of major importance. Some cases will experience little difficulty in maintaining a cold resistant state of

health; others will need to give more attention to one or more factors associated with readjustment to maintain the same state of health. We are unable at this time to evaluate these separate factors. We have suggested the hydrotherapy first; then the diet control and have found most cases are benefited. The nasal vasomotor response returns to the normal pattern. There is an absence of head colds and what is of equal importance, the subjects enjoy a better state of well being and continue these hygienic practices for this reason. Recurrences of colds, in the absence of undue exposure, indicate a lack of proper adjustment and require investigation. The mental factor frequently is found important in such instances.

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Functional Disorders of the Gastro-Intestinal Tract: the "Gastro-Intestinal Neuroses"*

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IT is indeed presumptuous to attempt to discuss a subject so broad as the functional disturbances of the gastro-intestinal tract in a brief presentation. It is probably literally true that one could present the field of surgery of the abdomen in the same period of time and do more justice to the subject. At least, with that topic one could omit the lips, teeth, tongue, mouth, pharynx and esophagus from consideration. Of necessity, I shall limit the discussion in this paper to certain generalities concerning the entire gastro-intestinal tract, and then attempt to deal only with

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three specific syndromes: namely, gastric disturbances, constipation, and diarrhea.

Indefiniteness of concept "Functional" applied to this group: In contrast to certain other uses of the term "functional," for instance, as applied to the heart or even to mental illness, the group of disorders of the gastro-intestinal tract can rarely be regarded as entirely "functional." Very often we find physiological disturbances such as the changes in the peristaltic activity of the stomach and the intestines; likewise, often there is disturbance in the chemical balance, referring particularly to the presence or absence of hydrochloric acid, as well as other gastro-intestinal secretions; and there are found even some relative anatomic changes in the position and size of the stomach, the location and convolutions of the intestines. There is probably no other organ system which shows such fine intergradations between "functional" and organic changes as those reflected by the gastro-intestinal tract. Probably more often than in any other set of organs in the body, do longstanding, so-called "chronic functional" illnesses result in structural changes in the tissues, as seen for instance, in the ulceration of the stomach, the duodenum, or the colon.

The prevalence: If for no other reason than the length of the gastro-intestinal tract, its functional disorders probably constitute the largest single group of organ misfunctioning in medicine. Next to the skin, the gastro-intestinal system has more contact with the outside world than any part of the personality. It receives more direct demands for adjustment and accommodation, more insults and abuses, and a greater variety of opportunities for gratification than any other set of organs suffers or enjoys. Such disturbances occur in every one of us, in some of us all too frequently. A large proportion of our patients come to us complaining chiefly of some disturbance of this portion of their anatomy. Most gastro-enterologists will agree that at least 50 per cent of the cases they see fall into the so-called "functional" group.

Attitude towards etiology: It seems almost paradoxical in the face of the prevalence of these disorders, that the layman should be so ignorant of the emotional factors producing them, and should have developed so many erroneous ideas about the supposedly normal functioning of the gastro-intestinal system. Among the most popular quacks are the naturopaths with their dietary fads, those who focus their attention on the distal three feet: the "colon specialists," and the "pile doctors." Perhaps it is even more paradoxical that the practitioners of medicine should give evidence of considerable confusion and uncertainty both as to the cause and the management of these illnesses.

There is an increasing recognition on the part of physicians that a "functional" difficulty in the gastro-intestinal tract is only an expression of a disorder in the personality. While recognizing this commendable trend, we must also face the fact that not very many physicians make practical use of such an understanding. A British doctor, Crookshank (1), has adequately expressed this apparent paradox in the medical attitude by stating, "It always seems to me odd in the extreme that doctors, who when students suffered with frequency of micturition before an oral examination, or who when in France had actual experiences of the bowel looseness that occurred before action, should persistently refuse to seek a psychological correlative —not to say an etiological factor—when confronted with a case of functional enuresis or mucus colitis. I often wonder that some hard-boiled and orthodox clinician does not describe emotional weeping as a 'new disease,' calling it paroxysmal lacrymation, and suggesting treatment by belladonna, astringent, local applications, avoidance of sexual excess, tea, tobacco, and alcohol, and a salt-free diet with restriction of fluid intake; proceeding, in the event of failure, to early removal of the tear glands. Of course, this sounds ludicrous. But a good deal of contemporary medicine and surgery seems to me to be on much the same level."

The confusion regarding the etiology is well expressed in the various causes ascribed to the "functional disorders" of the gastro-intestinal tract. I hasten to add that in part, some of these are probably correct, and certainly we are not justified in saying that they are entirely wrong. Referring, for instance, to only one disorder, the so-called "unstable colon" has been described variously as being due to avitaminosis, allergy, intercurrent infections, mental strain, spasmophilic diathesis, autonomic imbalance, nervous strain, endocrine disturbances, dietary deficiencies, or constitutional factors, as well as to a whole series of anatomical anomalies of the gut. Regarding the latter a prominent gastro-enterologist, Palmer (2), has expressed this opinion, "Much has been written of the redundances and loopings, of mobile and immobile cecums, of high-lying cecums, or low-lying cecums, of autonomic imbalance, of visceroptosis, etc. It is necessary to maintain a critical and somewhat skeptical attitude towards all this innovation."

I may interject that the progressive attitude of the gastro-enterologist is shown in Palmer's further opinion of regarding such individuals as having a "barometric abdomen," which is only an indication of the total personality, and that "attention should be directed not to the bowel alone but to the total personality of the patient."

If the attitude towards the etiology as evidenced by the causative factors ascribed to these conditions is confusing, the terminology is quite hopeless. Considering the stomach alone we can find classifications of the sensory, motor, and secretory disturbances, all of which fall under the more general categories of "reflex dyspepsia," or "nervous dyspepsia." In standard textbooks (3, 4) I have found included under the sensory disturbances such diagnostic groupings as "gastric hyperesthesia," "gastralgia," "mental anorexia," "anorexia nervosa," "bulemia," "gastric obsession," "pseudogastropathy," "dilatation of the stomach," "sitophobia." Under the so-called "motor neuroses" are included "nervous eructations," "nervous vomiting," "rumination," "pylorospasm," "hyperkinesis," "aerophagia." Under the "secretory neuroses" are included "hyperacidity" and "hyperchlorhydria," along with "hypersecretion," "hypoacidity," and "gastromyxorrhea." If one wished to review the many terms that are used and have been used in the past for intestinal difficulties one could literally find hundreds. Sullivan (5) reported in his extensive survey of mucus colitis that 35 different terms have been applied to this one particular syndrome.

What can one conclude from these formidable lists, were they completed, of etiological factors and terminology? Only that we are forced to use unsatisfac-

tory descriptive terms of a local condition which at most is only one very small part of a total personality disturbance.

The theory of psychogenic etiology has received widespread recognition. Even in our everyday language there are many phrases which indicate a relationship between the personality traits and various parts of the gastro-intestinal tract. Thus, we speak of a "sucker" as the man who "bites" on something and is fooled; we designate certain persons as "leeches" because of their hanging-on propensities. We speak of a person "sinking his teeth" into a job; we speak of not being able to "stomach" something, of "guts" and "intestinal fortitude." Everyone is familiar with the phrases of having a "belly full" and of "biting off more than one can chew." There are a great many vulgar words and phrases for feces which are used colloquially to indicate depreciation or disparagement or hate. In all of this language the layman recognizes a definite relationship, even though intuitively and unconsciously, of the significance of the gastro-intestinal tract to the development of the personality.

The general practitioners, the internists, and particularly the gastro-enterologists almost unanimously accept the existence of some such relationship. In general, there are three classes of reactions shown by these groups. First, there is a group of "die-hards" who take the attitude that the chronic intestinal ulceration causes the personality change; they are prone to get into arguments as to whether the hen or the egg came first. There is a second group, a large number of physicians (6, 7, 8, 9, 10, 11), who concede the psychogenicity of the "functional" disorders of the gastro-intestinal tract, but who use vague terms to refer to the psychological components, such as "emotional disorder" or "worries," or "anxiety"—and assume that these explain the problem. An example from one of our leading textbooks serves as an illustration. A brief discussion on "nervous dyspepsia" ends with the remark, "Practically all of these cases are psychogenic and the treatment is psychotherapy." The next paragraph takes up a new subject. To the critical psychiatrist this is equivalent to saying that "the disease is hematogenic and the treatment is hemotherapy." Thus, an excellent gastro-enterologist like Alvarez (12) in his justly popular treatise "Nervous Indigestion," divides the functional diseases of the digestive tract into "fatigue neurosis," "temperamental indigestion," "anxiety neurosis," "mental infelicity," "nervous vomiting," and "psychopathy." Such terms are just as vague to the psychiatrist as "stomach trouble" or "bowel disorder," and the psychiatrist who employed gastro-intestinal terms of comparable age and inexactness in a paper would receive little mercy at the hands of a reviewing internist, and rightly so.

There is a third group of physicians, small in number, who have made it a special point to study the personalities of patients with these difficulties. Outstanding in this group is Draper (13) who has made a detailed evaluation of the personality reactions in individuals with gastric ulcer. Similarly, Sullivan (5, 14) has approached the problem of ulcerative colitis with excellent therapeutic results. With perhaps a little less detail in the personality evaluation, studies have been carried out by Oppenheimer (15), Underwood (16), Diamond (17), Palmer (18), and probably others.

WHAT CONTRIBUTION HAS PSYCHIATRY MADE?

Unfortunately, except as gastro-intestinal disturbances occur in his neurotic and psychotic patients, the psychiatrist has had little opportunity in the past to study this group of problems. Of some fifty papers written in the past few years on this subject by internists and gastro-enterologists, I did not find a one in which it was recommended that the aid of a psychiatrist was necessary, even though the great majority specified agreement that the illness was psychogenic. In Alvarez' book "Nervous Indigestion," referred to above, there is not a single reference to a psychiatrist, and in the reading list given there are no psychiatric writings included. Why does this lack of cooperation exist? It is not the purpose of this paper to find the reason. It may be that the majority of internists are not aware that they might obtain any help from the psychiatrist, and on the other hand, this may be in part the psychiatrist's fault because for so long he had confined his interest and the subjects of his papers to the "insane."

There have been some contributions by psychiatrists (19, 20, 21, 22) which are of much interest to the general practitioner and to the internist. The most detailed study and the most helpful understanding of a limited number of these functional disorders of the gastro-intestinal tract has come from the Institute for Psychoanalysis in Chicago (23), under the direction of Franz Alexander. Two years ago they published the first results of their study, and a brief summary of their approach and the findings indicates the contribution that may be expected in gastro-enterology from psychiatry, and particularly from psychoanalysis.

In this research problem at the Institute for Psychoanalysis the gastro-enterology department of the University of Chicago cooperated by referring certain well authenticated cases of gastric disorder, particularly ulcer, diarrhea, and constipation, for psychoanalytic study and treatment. Some of the cases were given psychoanalytic treatment but a larger number received only psychoanalytic study. Early in their study these workers were impressed with the constancy and similarity between the nature of the psychological conflict and the type of gastro-intestinal disorder. It was possible to describe the patient's emotional trend in terms of the three elemental tendencies applicable to both the psychological conflict and the gastro-intestinal symptoms, of first, the wish to receive or take as related to stomach disorders, second, the wish to give or eliminate as applying to the diarrhea cases, and third, the wish to retain as applied to the constipation cases.

Gastric disturbances: In the psychological development of the infant, it is apparent that his first interest and aim in life is concerned with the taking in of nourishment. The infantile wish to receive, to be taken care of, to be loved, to depend upon someone else, is most ideally gratified in the parasitic situation of the sucking infant. Thus, these emotional qualities of receptivity—the wish to be loved and taken care of—become closely associated in an early period of life with the physiologic functions of nutrition. Being fed is thus equivalent to being loved. The character attributes of the adult individuals with gastric dis-

order were found to be ambition and aggressiveness, and such persons often had effected considerable accomplishment. They consistently displayed a striving to be independent, active, and efficient. An investigation of the unconscious desires of these individuals, however, showed without doubt that this marked desire for independence, ambition, great self-assertiveness was an over-compensation. That is, the individual had to lean over backwards consciously, to completely repress or deny his unconscious wish to be dependent, to be loved, to be fed. This mechanism of over-compensation can be seen in many instances in life when the individual must consciously stress one point of view or desire, to neutralize an unconscious opposite point of view or desire. Such reversals are frequently seen in the personalities of individuals with psychoses, who in their normal life are exceedingly thoughtful, kind, pleasant and clean, but in their psychoses are extremely impolite, hostile, dirty. In the individuals with gastric neuroses it was thus apparent that this unconscious desire to be loved and to be dependent was in the primitive mind directly associated with the child's first form of love, namely food and nourishment. The gastric symptoms are thus presumably caused through these unconscious tendencies which serve as chronic psychic stimuli of the stomach, independent of the process of nutrition. Consequently, a peptic ulcer *per se* has no psychological significance, representing only the end results. On the other hand, the chronic hypersecretion and hypermotility which may lead to the ulcer are produced by the continuous unconscious desire to be fed.

Colitis Studies: In the group of cases showing diarrhea studied at the Institute for Psychoanalysis, the general conscious attitude expressed by these individuals was verbalized about as follows: "I have the right to take and demand because I give sufficiently. I do not need to feel inferior or guilty on account of my receptive and grasping wishes because I am giving something in exchange for them." In this conscious attitude there is apparent again the parallelism between the nature of the disorder, namely, diarrhea and the person's attitude toward life, particularly as it is reflected in his relations with other people, in that the diarrhea was found to be a substitute for giving something of real value, for making real efforts, and being actually active. It was also found to be a method that the individual could use to express hate. This hate or aggressiveness was mentioned above as being recognized even by the layman as exemplified in the colloquial expressions, using the vulgar terms for feces. In the individual with colitis it was thus found that the content of the unconscious psychic stimuli which caused the dysfunction were in some instances giving as a method of restitution for taking or receiving, and in other instances, aggressive elimination.

Constipation Studies: In the cases studied with constipation, the individual's emotional attitude to his environment could again be expressed in terms that applied equally well to his psychological problem—namely, to retain or to hold on. The conscious attitude as discovered in these individuals included a pessimism towards receiving help from others or depending upon them. They seemingly do not expect anything from anyone in contrast to the optimistic attitude of the gastric type. At the same time, however, there is a more or less conscious, very extreme sense of obligation to give, of which the patient tries to rid himself by renouncing all conscious tendencies to receive. Thus the conscious attitude is summarized as, "I do not take or receive and therefore I do not need to give."

The unconscious dynamic background of the symptom seems to be based on the rejection of the obligation to give on account of a fear of loss, but on the other hand, if he is forced to give, his gifts are of no value. The result of these two stimuli serve as a chronic inhibition of the intestinal peristalsis and result in the constipation.

In all of these types of cases—namely, the gastric, the colitis, and the constipation—these research workers have not claimed any finality about their findings. They believe that the dynamic relation of the individual to his environment cannot necessarily be reduced to these three groups of alimentary tendencies. Their findings, however, are highly significant in showing the specificity of the unconscious demands of the individual and the very likely possibility that the gastro-intestinal tract is affected by these chronic stimuli. They stress the fact that an adequate knowledge of the causative factors, namely, the unconscious desires, can be obtained only during psychoanalytic treatment of patients and by no other method. Furthermore, the patient's immediate life situation has usually only a precipitating influence on the disturbance, and his conscious attitude plays a subordinate role in the causation of the symptom. From their study it is the repressed tendencies, the unconscious desires, that serve as a constant stimulation and thus cause chronic dysfunction of the organs.

THE MANAGEMENT OF FUNCTIONAL GASTRO-INTESTINAL DISTURBANCES

Again, it is probably presumptuous to attempt a discussion of the treatment methods to be used in such a wide variety of manifestations of personality disorder. Perhaps in view of the fact that the psychiatrist rarely sees these cases, that is, that the general practitioner and internist rarely refer them, it indicates that the latter group can handle the majority of such instances in an adequate fashion. On the other hand, as judged by the reports of internists and gastro-enterologists in the literature and in textbooks, one gets the impression that their conception of dynamic principles of psychiatry is somewhat limited. Furthermore, from the long list of diagnoses and the long list of etiological factors, one may conclude that much confusion exists. For these reasons perhaps it is justifiable that occasionally a psychiatrist "speak his piece" about the treatment of such illnesses.

Regardless of what particular methods or procedures one is going to use, it is essential that he start with the premise that the physician is going to treat the individual and not the organ. If this axiom be kept in mind, the entire contact with the patient will be materially influenced, including the anamnestic interviews, the examination, and the subsequent management. At no time can we become so interested in the stomach mucosa or in the position of the colon that we lose sight of the fact that the patient himself is our primary interest and that his symptoms are only the mirrored expression of his maladjustment.

Psychotherapy: I have already complained that the textbooks are too prone to recommend psychotherapy without giving either explanation or direction, with

apparently the tacit assumption that the physician knows just what this is and how to apply it. Even in some of our most carefully reported studies, such as Sullivan's (14) on the psychogenic factors in ulcerative colitis, there is reference to psychotherapy as *the* method of treatment, but there is no explanation as to what form of psychotherapy was used, whether it was counselling, whether it was merely gaining confidence, whether interpretations were given, whether the unconscious motives were made conscious or what. Sullivan inferred that his patients, in many instances, were relieved entirely of their symptoms in the course of two or three months, but he did not state whether the psychotherapist saw the patient daily or weekly, or for five minutes or for an hour. This is not to be construed as a criticism because obviously the import of his paper was to point out etiology and not treatment, though it would be helpful to know in more detail about the methods of a man who has apparently been so successful in the treatment of such conditions.

Perhaps the particular type of psychotherapy (i e., whether it is expressive or suppressive, whether it is brought about through suggestion or persuasion or command) is not very important since every physician is largely guided by his own personality makeup in the administration of such treatment. It may perhaps be helpful to point out certain pertinent facts in the management of the psychotherapy of these particular kinds of difficulties that can be used by the average physician.

The Anamnestic Interviews: Previously I have attempted to point out the great importance of the initial contact of the physician with the nervous patient. These individuals as a group take themselves seriously, and particularly their illnesses, and consequently the anamnestic interviews are of tremendous importance. They are important because if the physician will give sufficient time and permit the patient to tell his story he gains two objectives: first, the cathartic value to the patient of reciting his difficulties (a procedure which previous physicians may have inferred was unimportant by a manifestation of impatience or busyness); and second, the establishment of confidence in the patient by giving this evidence of his sincere interest. During these interviews it is unwise for the physician to attempt to explain or give advice; his chief function is to listen.

Likewise, it is important that the physician should use care and patience to make a thorough, detailed physical examination, even if he is convinced in his own mind that the difficulty is entirely functional. By so doing he will impress the patient with the fact that he knows his status, and what he (the physician) may say later will have much more weight and consequently more influence with the patient.

However, to obtain a careful history of the patient's past physical health and the development of his present illness, and to make a careful physical examination, rarely puts the physician in a position to evaluate the psychological component in the illness. His own experience may tell him that this psychological element is there, but what it may mean in the life of the patient cannot be determined from such data. Only as the physician gains the patient's confidence can he learn of the past struggle, what the conscious anxieties may be, of the patient's life situation with regard to family, friends, and business. One can be sure that the patient with such complaints "suffers" far more than the individual with physical illness. It is probable that he suffers from discouragement or fatigue, or from weakness, fogginess, or fears.

The physician may rightfully ask, Why doesn't the patient tell me this in the first place? Why does he spend all his time talking about his abdominal complaints? Alvarez (24) has answered this question bluntly. "I can offer several excuses for him. One is that he soon finds that the average physician will not listen patiently to accounts of psychological troubles or vaguely described sensations. Often he is uninterested, incredulous, and without understanding or sympathy; often he scolds; he gives the patient the impression that he believes that he is imagining it all; he gives a prescription for a sedative and terminates the interview. Soon the victim learns to keep quiet about the psychic distresses and even to conceal them. Instead he talks about the one thing that he has found will interest the doctor, that is the abdominal discomforts. Unfortunately, he ends by overdoing it and soon he enters the hospital to get the first of a set of linear scars on the abdomen."

Once the physician has gained the patient's confidence, has learned what the vague sensations may be, what the fears or doubts or the troubles are that exist in his life (apparently quite independent of the physical complaints), then, and only then, is he in a position to make any suggestions relative to environmental changes or alterations in the relationships in the home or the business. Always in such instances must the physician be the counsellor in regard to the patient's life situation, and not merely the doctor for his "guts."

The psychotherapy may well include a certain amount of education—education in the sense of enlightenment about the gastro-intestinal life, the ways in which the gastro-intestinal tract can reflect the experiences and relationships and emotions of the individual. Furthermore, the physician is never in a position to evaluate the entire significance of such problems as these until he knows of the patient's sexual life. In a surprising number of instances there is a direct relation between the sexual practices, or, in some instances, the desires, inhibitions, and fears, and the gastro-intestinal symptoms. Again, in many instances, simple education may change the entire picture for the patient.

The obtaining of the anamnestic interviews, the evaluation of the psychological component in the patient's life situation, and the educational procedures are all forms and applications of psychotherapy. Such a procedure is not a matter of an hour but can certainly be expected to take many hours. One cannot set a definite time limit for these interviews, since in some instances the patient may respond in the course of two or three interviews, and in another instance, may not respond over a period of weeks or even months.

Perhaps it is this latter group with which one needs expert help, namely, the help of the psychiatrist. As far as the application of psychoanalysis is concerned, each case must of necessity be judged by its own merits as to whether this form of treatment would be helpful. From the psychoanalyst's point of view he is glad for an opportunity to study such patients, and a fortunate corollary is the therapeutic success in a high percentage of cases. But the application of

psychoanalysis is limited not only by the nature of the illness but by the fact that it is a long, often difficult, procedure which presents the economic problems of time and expense for the patient.

TREATMENT OTHER THAN PSYCHOTHERAPY

It is not to be inferred that the psychiatrist would assume for a minute that psychotherapy was the only treatment to be used in the functional disorders of the gastro-intestinal tract. So long as we follow the principle that we are treating the patient and not his particular organ, any method may be used to further this aim. As a consequence, various procedures and drugs may be used which in themselves are to be regarded as a kind of psychotherapy, and so long as they are used from this point of view they can be helpful. There is nothing contradictory to the use of psychotherapy along with the prescription of a regime or drug or physiotherapy or dietary recommendations, so long as these measures do not lead the patient to affirm his belief in his sick organ or a structural defect in his system. On the other hand, when they do lead the patient to such conclusions they are detrimental and become antagonistic to the principle that the patient is sick and not his organs.

The psychiatrist occasionally sees cases in which attention to the general physical condition is in order before psychotherapy is given. I am referring particularly to that type of nervous dyspepsia in which the individual loses weight rapidly and extensively. We recently had a patient who over a period of a year had lost in weight from 130 pounds to 68 pounds. She was so weak and emaciated that she could not lift herself from the bed. Drastic measures are always in order in such instances and psychotherapy follows. The prescription of all accessory methods of "psychotherapy," if we are to regard drugs and diet as such, however, cannot replace the desirability of determining the psychological component in the illness.

1. *Prescription of a Regime:* A regime of exercise, relaxation and rest if too rigid or over-emphasized may do harm. It does harm because it adds to the patient's illusion. It leads him to believe that his difficulty occurred because he has failed to take exercise, or because he doesn't get enough rest, or because he doesn't know how to relax. In part, these may be true, but the danger lies in letting the patient find a temporary escape in such corrective measures to the exclusion of the recognition of his mismanaged emotions. It is probably always safe to help the patient see that he doesn't get sufficient rest or exercise and in a great majority of instances the intelligent individual can be led to such conclusions without the physician's command being necessary.

2. *The Prescription of Drugs* in functional disorders of the gastro-intestinal tract is a temptation fraught with much danger. If a physician expects to treat the personality of his patient he cannot rely on the pharmacological action or the magic suggestion of the drug to make any very radical changes in the personality. Any drug should probably be used incidentally, and at most temporarily, depending upon the intelligence of the patient and the physician's judgment as to how much he can understand. It is perhaps often practical to "debunk" the patient regarding the magic of the drug, to explain specifically what it is, the temporary relief to be gained, the rationale for its momentary usage. Always should medication be interpreted as a temporary crutch, and if the patient has such an understanding the physician is justified in prescribing sedatives such as triple bromides or barbital for insomnia; likewise, carminatives for flatulence, intravenous glucose for vomiting, or insulin for anorexia. But he must use these guardedly, knowing that the patient's tendency will always be to capitalize on them and thus avoid solving his major problem of emotional disharmony.

3. *Dietary Recommendations:* In his dietary recommendations to the individual with gastric disorder or colonic difficulty, the physician is always in the predicament that if he stresses the necessity of a particular diet, he is likely to apparently deny the psychologic nature of the gastro-intestinal disturbance in the patient's mind. As a consequence, probably a majority of gastro-enterologists who direct their treatment in such cases to the total personality, suggest that as nearly a normal diet be prescribed as is possible. In other words, there is a fairly uniform condemnation of vegetarian or roughage diets. Here again, it seems practical for the physician to depend to a considerable extent on the patient's intelligence. If the patient is underweight and recognizes the fact, it is frequently possible to learn from him that he knows which are rich foods and which are likely to increase his weight. If he needs education about dietary matters the physician can give this chiefly as a matter of education and not of necessity specifically applying it to the patient. In other words, the more nearly the physician can help the patient to accept a normal diet and "debunk" fad diets and educate him in dietary facts, the more closely will treatment be in accord with our principle of treating the patient and not merely the gastro-intestinal tract.

4. *Physiotherapy:* Physiotherapy can be used ideally as a method of psychotherapy. The use of massage or ultra-violet ray can, if used along with suggestion, be directed in all instances to the general personality and not to the specific organ affected. Such an interpretation, however, does not hold true when applied to colonic irrigations, and there seems little to support the usage of this procedure, either for psychological therapy or physiologic benefit. Such treatment strikes a death blow to the physician's thesis that the symptoms are an expression of a personality disorder and not merely a colonic disease. Occasionally enemas are desirable, in fact necessary, but to make the habit into a daily ceremony is placing undue emphasis on a part to the detriment of the whole. The psychiatrist also recognizes that in some cases colonic irrigations and the enema habit have great significance in the unconscious. It is often apparent that some individuals, although complaining constantly, get obvious satisfaction from this prescribed and therefore approved "attack from the rear."

5. *Operations:* It is needless to say that operations are never indicated as a treatment for functional gastro-intestinal disorders. The subject is mentioned here not only to indicate that they are not good therapy, but particularly to call attention to the fact that a fair percentage of patients with these disorders demand operations. My brother, Karl A. Menninger, has dealt with the subject extensively under the title of *Polysurgery and Polysurgical Addiction (25)*. Alvarez (24) reflects a practical point of view on the problem. "All credit to physicians who try to talk these patients

out of the idea of an operation. You try to show them the truth but it takes so much time that it is usually hours; and often you are almost certain that all the patient will do is shop around until a compliant or a not overly-careful operator is found. Under such circumstances it is human to say to yourself, 'If the operation is going to be done anyway, perhaps it would be better that I do a good job and explore carefully than to let the patient run the risk of falling into the hands of some poorly trained man who will not explore or who may do great injury.' This is a dangerous reasoning and personally, I hate to yield to it. He who slips too easily along this path will end by losing his scientific soul." Further on, the same author states, "Often, the physician who doubts the wisdom of operating has attempted to console himself with the feeling that if he does permit the removal of the appendix at least he will do no harm. Would that this were always true. It may be true for a person with a normal mind and normal nerves but it is not true for many psychopathic and oversensitive persons. In them the harm done by needless operations is often terrible and irreparable; the abdomen never feels right again; new pains appear; some physician is found who rids himself quickly of a time-consuming patient by making a diagnosis of 'adhesions'; more operations are performed and finally we find the husband ruined financially and the wife lying on a couch, a hopeless invalid."

SUMMARY

An attempt has been made in this paper to present a psychiatric point of view regarding the functional disorders of the gastro-intestinal tract. That such disorders are primarily emotional in their causation is a fact granted by nearly everyone. The point is stressed, however, that such individuals should have the benefit of an accurate, penetrating, and detailed analysis of the psychological component in their illness, and that only as we understand the dynamic aspect of the personality disorder can we adequately treat the individual. Treatment in all cases must be directed towards the total personality and not towards the stomach or the intestine or the colon.

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Studies on Autodigestion, VII. Is Digestion of the Living Tissues (Claude Bernard's Experiment) a Local Phenomenon?*

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THE following work tries to answer the question whether the digestion of parts of a living animal as first demonstrated by Claude Bernard is a local phenomenon, or whether such changes occur in the blood of the animal that would tend to lower the resistance of its tissues to digestion. In previous papers the literature pertaining to and the theories about resistance of living matter to digestion have been reviewed (1-6), and will not be repeated here. During the course of this previous work the hindlegs of a number of anesthetized or pithed frogs were exposed to N/10 HCl or N/10 HCl with 2% pepsin 1:10,000† for 1-2 hours. In the first group no digestion occurred, in the second group either skin or skin and muscle were digested. While most animals of a control group (anesthetized only) survived, all frogs exposed to HCl or HCl pepsin, died within 12 hours. The rapidity of digestion was found to depend on the extent of surface

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area exposed to acid pepsin (5). These two observations pointed to the possible occurrence of systemic rather than local changes and prompted the following experiments. Bullfrogs (rana catesbiana), albino rabbits and Belgium hares, and dogs were anesthetized (bullfrogs: urethane; rabbits: morphine + urethane; dogs: pentobarbital sodium) and both hind legs (hair being clipped first) exposed to pepsin HCl (N/10 HCl, 1% pepsin 1:10,000) only or alternately to alkaline trypsin (.25% Na_2CO_3, 2% 1/200 trypsin†) and acid pepsin. The digestive solutions were kept at 38° C. Blood was withdrawn from the carotid artery or, in the case of bullfrogs, from the aorta. Only such observations are reported in which at the termination of the experiment the animal was living and as viable as during the control period. Blood was withdrawn before exposure to the digestive fluid and after digestion had occurred. Some animals were anesthetized only and blood was withdrawn at intervals similar to those in digestion experiments. In case of the rabbits the volume of blood withdrawn was replaced by heparinized rabbits' blood.

The pH of the blood was determined with a glass electrode. Plasma CO_2, blood O_2 content and capacity, N.P.N. and total chlorides were estimated by the usual methods (7).

RESULTS

A. Bullfrogs: Six animals with an average weight of 660 grams each were anesthetized and exposed to pepsin HCl. Considerable digestion of skin and musculature occurred. Plasma CO_2 dropped from an average of 62 volumes % (56-68 vol. %) to an average of 44 volumes % (31-49 vol. %). In one control animal which was not exposed to pepsin HCl the same change of plasma CO_2 took place (from 65 to 44 vol. %). Changes in pH were small and inconstant.

B. Rabbits: Nine rabbits, weighing from 1.8 to 3.6 kg. were used (average weight 3 kg.). The rabbits exposed to HCl pepsin showed little or no digestion of their skin. Those exposed alternately to pepsin and trypsin solutions (1-2 hours in each) had considerable digestion of their skin and musculature and frequently bled abruptly and fatally from corroded arteries (Figure 1). Such lesions were multiple and no region of predilection could be detected. Changes in pH were inconstant. In 5 animals a decrease occurred (from 0.02 to 0.35, with an average of 0.1) and in 3 animals an increase of pH was found (from 0.02 to 0.1, with an average of 0.07). Blood CO_2 decreased in 8 animals (from an average of 48 to 38 vol. %). In one animal it rose from 44 to 52 vol. %. O_2 tension and capacity of the blood did not change materially in those animals which had no appreciable bleeding from corrosions. Total Cl and N.P.N. of the blood were done on 3 rabbits. The Cl rose slightly but insignificantly in all three instances—viz, from 524 mgm. % before digestion to 537 mgm. % after 13½ hours of digestion; the N.P.N. was variable, falling from 54 to 40 mgm. % after 10 hours of digestion in one experiment, whereas in another N.P.N. rose from an initial value of 50 mgm. % to 64 mgm. % after 13½ hours of digestion. Three rabbits were anesthetized only and showed similar changes of pH, CO_2, O_2, Cl and N.P.N. as in the case of the digested rabbits described above. Skin from digested areas was examined histologically, and localized ulceration, hemorrhages, hyalinization, and disintegration of the fibrous and adjacent muscular tissues observed; no thrombi were seen in blood vessels. Three rabbits were exposed alternately to HCl pepsin and alkali trypsin until small ulcers appeared in the skin, and then were put back into their cages; no untoward effects were noted, and the animals were well one week later.

C. Dogs: A four year old male dog of 6.5 kg. was anesthetized and the right hind leg was placed in acid pepsin solution for four hours on one day and for 7 hours on the next day without any signs of digestion nor any later untoward effects to the dog.

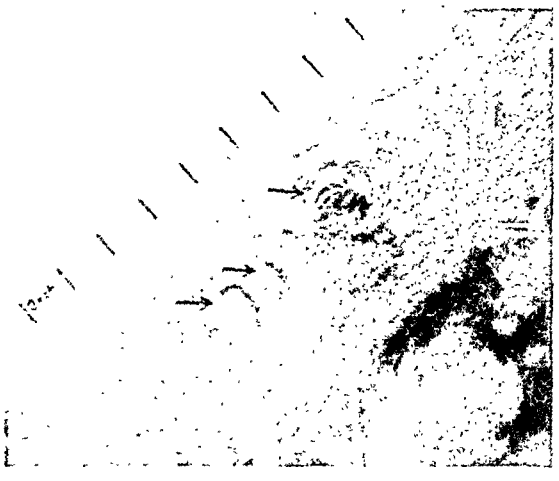


Fig. 1. Leg of 3.5 kg., female, albino rabbit after eleven hours of alternate exposure to pepsin and trypsin solutions. Exposed blood vessels in upper one of three ulcers.

DISCUSSION AND CONCLUSIONS

All such changes as occurred during digestion in pH, O_2, CO_2, Cl and N.P.N. of the blood were not specifically due to exposure to acid pepsin and alkali trypsin, but probably were due to the anesthetic and to prolonged exposure of the animals. While frogs died after such exposure, rabbits and a dog did not, and no after-effects were noted. No appreciable diffusion of H ions took place through blood or lymph vessels whose permeability might have been changed by the digestive media. It is unlikely that anoxemia was present in the limbs exposed to digestion. Erosions of small arteries and veins bled profusely, indicating no appreciable impairment of circulation in the legs. We conclude, therefore, that Claude Bernard's phenomenon of the digestion of the leg of a living animal is explainable as a local necrosis of tissues with subsequent digestion. This local necrosis can be performed by HCl alone without pepsin, and subsequent application of acid pepsin or of alkali trypsin will then produce digestion (6). Alternating acid pepsin and alkali trypsin was found to digest more rapidly and more intensely than acid pepsin alone, thus confirming previous work (6). Our above findings support those of Dragstedt and Vaughn (8) and our own (6), that the rate of digestion depends on the concentration of HCl in the HCl pepsin solution (in both reports the HCl concentration was within physiological limits). The above results do not explain why in frogs digestion is faster when more surface is exposed to acid pepsin solution. It seems however, that anesthesia and exposure damage the frog to a high degree. Dog

and rabbit survive anesthesia and exposure and even slight digestion of their skin without noticeable after-effects, and therefore results on these animals seem to be more fit for interpretation of the phenomenon than those on frogs. It seems to us that no inference can be drawn from the above experiments as to the genesis of gastro-duodenal ulcer. Unlike the skin, gastric and duodenal mucosa have a specific resistance against acid corrosion and decrease of viability seems to be the additional necessary factor leading to ulceration (9).

SUMMARY

In anesthetized bullfrogs, rabbits and a dog the effect of peptic and tryptic digestion of the hind legs on blood pH, CO_2, O_2, Cl and N.P.N. was observed. No constant significant change was found and the conclusion is drawn that Calude Bernard's phenomenon can be explained as slow acid corrosion and subsequent digestion of devitalized tissues. The results confirm the necessity of assuming an additional factor (devitalization) of tissues in the occurrence of gastro-duodenal ulcer. Alternation of peptic and trypic digestion greatly increased the rate of digestion.

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Editorials

THE ATTITUDE OF THE ASSOCIATION TO NEW MEMBERS

INTEREST in gastro-enterology is rapidly increasing; the specialty as a sub-group of internal medicine has, in the last 20 years, made creditable advance both from a clinical and scientific standpoint.

Many of the younger men interested in this specialized field of medicine are ambitious in their efforts to attain membership in the American Gastro-Enterological Association. It is the desire of the Association to encourage and foster that ambition and to choose from aspiring candidates those who are best qualified to fill the occasional vacancies in the limited membership of the Association that arise as the result of deaths, transfers to Senior membership and advancements from Associate to Active Membership.

Candidates are judged on their scientific and clinical achievements, the position attained in their local community, hospital, school, their scientific publications, by their moral and ethical standards and their personal qualifications.

The Executive Council of the American Gastro-Enterological Association desires to encourage candidates for membership in the Association by announcing that the "American Journal of Digestive Diseases and Nutrition" will be glad to consider for publication contributions on clinical, laboratory, or scientific subjects dealing with gastro-enterology, metabolism, or nutrition.

Contributions of merit will be accepted for publication and, thereby, will assist the candidate in bringing to the attention of the members of the Association the type and character of the work he is doing. Contributions submitted for publication in the Journal should be sent to the Editor, Dr. Beaumont S. Cornell.

Burrill B. Crohn, New York, N. Y.

SOME DANGERS INVOLVED IN LEAVING ULCER PATIENTS TOO LONG ON A STRICT DIET

THE old injunction to physicians to cure safely and without doing harm needs still to be remembered today. When during one week a physician can see three patients who have been brought to the brink of serious disaster with pellagra or scurvy by the long continuance of an overly strict ulcer diet, it is time that gastro-enterologists did more to warn the medical practitioners of this country against this danger to their patients. Naturally, it is not always the practitioner who is at fault: he may never have intended the patient to stay for months on the strictest diet, but the man did not return to report, and so damage was done.

In many cases, however, when a patient with ulcer is doing badly, and especially when he has bled severely, it is natural that his physician should exhort him to be particularly strict with the diet. It is a natural reaction also on the part of some patients to conclude that if some deprivation in the matter of eating is good more should be better. If they get along fairly well they will not see the need for returning for a check-over, and in a year or so one is likely to find a pale sickly looking patient who is still living on a soft diet consisting largely of milk, cream and cereal. When, as sometimes happens, the milk has been boiled so as to destroy what little vitamin C it contains, it is hard to understand how the patient has escaped coming down with frank scurvy.

Unfortunately, also, for the patients who have bled badly and who need to build much hemoglobin, the probably needlessly strict but commonly used type of ulcer diet without meat does not contain much iron. Recently, the writer saw a woman with ulcer who had bled until her hemoglobin reading was around 50 per cent. Because she was so frightened she was glad to

stay on the strictest diet her physician would give her, and for months she lived on little besides milk, cream and cereal. Unfortunately her physician did not happen to remember that years ago Whipple and his assistants showed that one could produce a uniformly fatal anemia in dogs with just such a diet as this woman was on. As one would expect, then, she not only failed to regenerate the blood she had lost, but she continued to go on down hill. And as if her adherence to an almost iron-free diet were not bad enough, she was taking alkalies which, as has recently been shown, seem somehow to block the absorption or usage of whatever iron is being given by mouth.

Of late, Carlson and Rivers* have been studying a group of patients with hematemesis, with or without definite ulcer, from the point of view that in many cases the bleeding may be kept up or even brought on by the injury to mucosal cells and capillaries produced by the marked deprivation of vitamin C which goes with overly strict dieting. It may be that some of these patients are suffering from mild and unrecognized scurvy. Certainly in the case of one of the patients just seen by the writer the amount of vitamin C in the blood was only 0.25 mg. when it should have been at least 0.9 mg. In this case the patient, while on the diet, developed a severe gingivitis which resulted in the loss of most of his teeth, and one wonders now if this might not have been part of an unrecognized scurvy.

Another point which was brought out by Snell and Wilbur at the recent meeting of the American Medical Association is that even when a patient is given the minimum requirements of vitamins in the diet he may still get into trouble if he has a malfunctioning gastro-enteric stoma with jejunitis or some other condition which produces a too rapid progress of food through the upper part of the small bowel. Under these conditions he may be able to absorb only a small fraction of the stock of vitamins with which he is being supplied. It would seem then that in all cases in which digestion in the upper small bowel is handicapped, the supply of these small dietary essentials should be increased rather than diminished.

Some of the good results obtained by Meulengracht with a full diet in the case of persons with gastro-intestinal bleeding might be understandable now if a certain percentage of his patients should happen to be suffering with a mild form of scurvy such as can be relieved promptly by a full diet.

Incidentally, how certain can we be that in cases of ulcer, the adherence to a strict diet between attacks will help in the prevention of recurrences? Certainly the discouraging stories which the gastro-enterologist hears in his office every week are hardly designed to reassure him on this point. Time and again he will learn that pain or bleeding returned when the patient was still dieting carefully and taking food between meals, and the older and more experienced he gets the less disposed he will be to promise a patient immunity to recurrences as a reward for the strictest adherence to an ulcer regimen. Physicians who have ulcer themselves know this, and many will say that so far as they can see, it doesn't make much difference what they eat between their attacks. The really important factor in bringing a recurrence seems often to be nerve strain and worry.

Partly, then, because it does not seem to pay well to diet very strictly and partly because a man with ulcer should maintain a good state of nutrition, it would seem as if we physicians could afford to be fairly generous dietetically with all of those patients who have a tractable type of ulcer.

Many able gastro-enterologists are afraid of giving raw fruit juices, and some absolutely forbid their use, fearing that the acid will do harm. Others do not worry about this possibility because the organic acids in fruits are so weak and are present in such small amounts that it would seem they can have very little effect in the way of activating pepsin. Compared with the hydrochloric acid in the stomach they must represent but a drop in the bucket. In a recent article (this Journal, 2:242-243) Kugelmass showed that orange juice has a pH about 3.0 and tomato juice about 4, but they contain very little free acid. They are really buffer solutions consisting largely of mixtures of the primary and secondary salts.

Some studies should be made soon to determine once and for all if there is any difference in the results obtained by patients who are and are not given raw fruit juices. Certainly if it is not dangerous to give these juices they should be included in ulcer diets so as to protect the patient from slipping into a condition in which he will be predisposed to hemorrhage.

Walter C. Alvarez, Rochester, Minn.

*Carlson, L. A., and Rivers, A. B.: A clinical consideration of deficiency factors of diets in the etiology of peptic ulcer. Rev. Gastroenterol., 4:250-271, June, 1937.

BACILLARY DYSENTERY

IN 1936, Dr. Arthur Hurst (1) of London, published in the Lancet, a paper in which he calls attention to the widespread distribution of bacillary dysentery in the British Isles and discusses the possible relationship of that disease to so-called non-specific ulcerative colitis. Dysentery of a specific bacillary nature exists in epidemic outbreaks in many localities of England; carriers surviving from the World War are numerous; in his opinion the etiological relationship of the two diseases is most often plausible if not often proven.

In this country, the United States Public Health Service is carrying on an investigation of this specific diarrhea. Particular attention is being given to New Mexico and Arizona. Preliminary observations suggest that the results will be interesting. These conditions are also being studied in Virginia. Some urban populations are also coming under close observation and examination.

If the relationship between acute outbreaks of infectious diarrhea, in camps, in institutions, on shipboard or in city communities is to be correlated with acute or chronic ulcerative colitis, if the scientific etiology and causal connection is ever to be clarified, it behooves every practitioner and specialist in medicine to study each colitis case for its possible infectious contacts, its exposure to other diarrheal cases, to possible carriers, and to centers and communities which may be harboring bacillary dysenteric endemics.

Even though stool cultures are individually negative, or serum agglutinations are inconclusive, the search must be constituted for possible contacts with carriers or distributing centers. In each family wherein a case of colitis occurs, a careful search for dysentery carriers should be instituted; members and

particularly the servants and food handlers should be questioned for their instances of contemporaneous diarrhea. One should diligently inquire regarding recent travels to possible states or countries where diarrhea is prevalent, to exposure to surface or unguarded drinking water, watered vegetables, shipboard diarrhea, or recent institutional sojourns. It is surprising how often it will be noted that some other member of the family, or one of the help, is also suffering from diarrhea, or how often significant grouping of other and similar cases suggests a locality infection. Most local Boards of Health will willingly cooperate in stool cultures of possible carriers or serum agglutination tests.

The problem of the association of colitis and bacillary dysentery is frankly before the profession for investigation and decision. There may be no relationship, or a relationship only in a small minority of cases, or there may be a significant connection. By wholehearted cooperation, by scientific willingness and alertness, an answer should be forthcoming or at least strongly suggested by this generation of clinicians, laboratory scientists, and public health authorities.

Burrill B. Crohn, New York, N. Y.

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AMOEBIASIS AND THE NEW YORK CITY WORLD'S FAIR

THE recent appearance of the official report (1) of the Joint Committee which investigated the Chicago epidemic of amoebic dysentery in 1933 in connection with the Century of Progress Exposition calls to our attention the fact that plans are at present under way for a similar event in New York City scheduled to open in 1939. This report again focuses attention upon the possible public health dangers inherent in the massing together of enormous numbers of individuals in a restricted locale within a short period of time.

This report is of particular interest to the gastroenterologist due to his intense preoccupation with acute and chronic infections of the colon. In their clinical investigations the committee found that although the great majority of cases had an incubation period from one to four weeks, there were a significant number of instances in which this was less than one week and occasionally was as long as three to four months or longer. Especially striking were the difficulties and uncertainties in the diagnosis of amoebiasis due to the frequent occurrence of clinical features usually considered atypical. Among these was the frequent absence of diarrhea and the very real difficulty of finding E. histolytica in the stool. Another confusing feature and formerly considered an unusual event in amoebiasis was the presence of fever which was observed in many cases and which was relatively high at times even in uncomplicated cases. The frequent occurrence of local rectal symptoms associated with induration and ulcer formation led to the erroneous diagnosis of malignancy of the rectum in a large number of cases.

In their beautifully thorough and complete analysis of the accumulated data the Joint Committee found that the disease, acquired in Chicago, had been spread to at least 400 cities scattered through 43 states, Hawaii, Canada and two European countries. They were able to trace 1049 cases in an obviously incomplete reporting of cases. This would indicate the magnitude and importance of the problem.

The committee was fortunately able to trace the foci of origin of the epidemic to two hotels which were found to be the major but not the sole sources of spread of the disease. A complete investigation of these two hotels revealed several interesting and important facts. Thus they found an incidence of the carrier condition among food handlers in the two hotels amounted to 34.3% in the one and to 57.3% in the other. They found that vigorous measures directed to the prevention of the spread of infection by carriers among food handlers were ineffective. Elimination of carriers of cysts of E. histolytica from among the food handling staffs was unsuccessful in controling the outbreak.

As a result of their extensive clinical, epidemiological and engineering studies they reached the significant conclusion that the principle if not the sole means of spread in the epidemic studied was through water polluted within one of the hotels. As a contributing factor they noted a progressively increasing number of carriers of E. histolytica among the employees and probably also among the guests who remained for more than a few days. In this way any "pollution of the water with hotel sewage would become progressively more hazardous." The committee points out that "the measures required to prevent the recurrence of such an epidemic are: (a) Effective supervision of the installation of plumbing in new buildings and of changes in old ones; (b) reasonably frequent inspections of the water and sewage systems of buildings, especially of the older ones; (c) particular attention to the elimination of hazardous cross-connections, through preventing their installation and through detecting and removing existing ones."

The indictment of engineering defects in hotel construction implied in the above does not remove the responsibility for their tolerance from the hands of the medical profession and the public health authorities. An excellent opportunity is at present afforded to the medical profession and health authorities to avoid a duplication of the Chicago misfortune.

Abraham Penner.

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PECTIN

A LITTLE over a hundred years ago a French investigator, Braconnot (1825) extracted some pectous material from plants; in as much as this material resembled a coagulum, he named it pectin.

Much work has been done on pectin since Braconnot's time. The water insoluble pectic substance is proto pectin, which is converted to water soluble pectin by enzymatic activity during the ripening of the fruit. If this hydrolysis goes still farther the methyl ester groups are split off and pectic acid appears as one of the substances associated with the decomposition of plant tissues.

It is generally agreed that these pectic substances are composed of a polymerization of galacturonic acid

anhydride as their basic unit and in addition there are arabinose, galactose, acetyl and methoxyl groups present. The latest work shows that unhydrolysed pectin contains an octagalacturonic acid nucleus.

It was customary to subdivide carbohydrates into those utilized and those not utilized; in other words, we have considered available and unavailable complex carbohydrate. The starches and sugars belong to the available, the hemicellulose, cellulose and pectic substances belong to the unavailable carbohydrates. The caloric value of the available carbohydrates is well known, but those not utilized are considered of little value except to form bulk or roughage.

The raw apple, the banana, and other fresh fruits have been administered with beneficial results to infants as well as adults with certain gastro-intestinal disturbances. The use of these fresh fruits has been more for therapeutic than for preventive purposes.

There are reports using apple and banana powder in place of the fresh fruit, with about the same, if not better results. Some authors have given pectin the credit for the improvement in the clinical picture in cases of diarrhea. Winters and Tompkins (*Amer. Jour. Dis. Child.*, 52:259, 1936) report better results with the use of a pectin-agar-dextrin-maltose formula than they obtained with the use of scraped raw apple in the treatment of infant diarrhea.

The galacturonic acid content of pectin has naturally been assumed to have a detoxifying action similar to glukoronic acid. Malyoth (*Klin. Wchnschr.*, 13:51, 1934), Riesser (*Schweiz. Med. Wchnschr.*, 16:1175, 1935), Manville, Bradway and McMinis (*Amer. Jour. Digest. Dis. and Nutrit.*, 3:570, 1936) and others considered this factor of importance in the action of pectin.

Imhaeusser (*Arch. f. exper. Path. u. Pharm.*, 167: 702, 1932) administered pectin to dogs and failed to find a rise in blood sugar. He also administered pectin to phloridzinized dogs and observed the same fatty changes in the liver as in the controls. This would indicate that no utilizable carbohydrates were derived from the pectin. There was, however, an antiketogenic action shown after pectin was fed to dogs, indicating that this substance was exerting some action and was not entirely unavailable, as had been assumed.

Banana and apple powder were used as carbohydrate source in the basal diet in some rodent experiments by Arnold (*Amer. Jour. of Pub. Health*, 24, No. 8:354, 1934). The control diets contained cornstarch or sucrose as their energy source. Rodents fed on the powdered fruit diets enjoyed a resistance to B. enteritidis administered by mouth as compared to the controls. The nature of this increased resistance to enteric infection was not determined. Such animals were very susceptible to the B. enteritidis when administered intraperitoneally or subcutaneously, but were resistant to oral feedings of these bacteria.

The so-called unavailable carbohydrates need more attention. The galacturonic acid component of pectin needs further study as to its detoxifying action.

The writer is convinced that pectin, as it is now available on the market, is not a uniform product. There is one very active carboxyl group attached to the pectin molecule. Most of the pectin on the market contains various positively charged elements attached to this carboxyl group, such as sodium, calcium, magnesium, etc., as well as arsenic acid and other insecticidal residues from sprayed fruits. The varying reports in literature may well be due to the use of various pectinates of this nature.

It is of interest to the gastro-enterologist to know that some of the so-called unavailable carbohydrates may, in part, be utilized in some way. The research workers in biology, chemistry, bacteriology and clinical medicine have new problems presented for their consideration.

Lloyd Arnold, Chicago, Ill.

Book Reviews

Medical writing. By J. H. Dempster, St. Paul, Minnesota, Bruce Publishing Company, 168 pages, 1937.

THIS is not just another handbook on medical writing, it is a delightful little volume which reflects on almost every page Dr. Dempster's rich culture, his wide experience as an editor, and his kindly philosophy and wit. It is the sort of book that one expects more from a cultured Regius Professor of Physics than from an American physician who commonly knows his medicine but seldom his Sir Thomas Browne, his Keats and his Charles Lamb.

As Dr. Dempster reminds us, writing makes an exact man. No other practice trains one in clear thinking to the same degree. Good writing is an art which a man can enjoy just as a painter enjoys a bit of painting, when at last he gets it just to suit him. As Lord Balfour once wrote, "What pleases me most is to write something quietly by myself—to touch it up and complete it with a feeling that one has really done one's best." How wonderful it would be if more American physicians were to get this thought about writing. Usually our main idea is to get a paper out of our system as quickly as possible, and later when some editor has to spend hours putting the manuscript into such shape that it can be printed and read, we become much annoyed over his efforts in our behalf.

As everyone knows who has ever tried to put his ideas across to others, easy reading means "damned hard writing." Dr. Dempster's comments about this remind the reviewer of the times when physicians have said to him, "If I could only dash things off as easily as you do I could get a lot of writing done." They didn't know that any paper that reads easily must always have been rewritten at least half a dozen times. Even the ablest and the most experienced writer can always find a better and clearer and shorter or a more vivid or musical way of saying a thing if he will spend some time trying.

Some of the chapters in Dr. Dempster's book which are not ordinarily found in works of this kind are those on the editorial functions, on preparing illustrations, on the use of the dictionary, on where to look for references, on Greek derivatives, on the history of medical journalism, and on copyright regulations. There is also a short list of books which can be read with profit.

The reviewer is particularly delighted to find Dr. Dempster approving of the occasional use of such things as a split infinitive. As he says, at times it is highly desirable that it be used. Unfortunately, an editor who sits all day correcting manuscripts tends to develop a number of reflexes which enable him or her to blue pencil certain grammatical constructions inevitably and without any cerebration. The experienced writer will follow no rule but will be guided always by his ear for good rhythm and accent in a sentence. If it does not *sound* right something is wrong and the arrangement of the words must be changed.

Dr. Dempster wisely quotes some unknown man who said that one good illustration is worth a thousand words of description. This holds true not only for drawings and photographs but also for verbal illustrations. One of the faults of medical writers is their tendency to write long sentences full of abstract statements the meaning of which may or may not be grasped after several careful readings. If the writer had only told a short interesting story about a patient or if he had briefly described one crucial experiment the reader might have gotten the meaning immediately and without the expenditure of much effort.

We physicians commonly make the same mistake in talking to patients. Too often we use long technical words, or worse yet, medical jargon about "flat plates" and B.M.R.'s, and the patient leaves with only the vaguest idea of what we were trying to tell him. More of us should practice talking to ignorant people in such simple speech that they can understand us. Wherever possible, we should teach as Christ did with the help of parables; we should use simple illustrations and similes, and should tell short stories of other patients with similar troubles whose experience taught them and the physician many things. Such stories will commonly interest and convince, and years later when the physician meets an old patient he may be surprised to find that some story that he told is still remembered together with the lesson that it taught. An abstract statement would probably not have been remembered for more than a few hours, if it was remembered at all. The same technic is useful also when one is talking to or writing for tired doctors. As a busy physician once said to the writer, "When I come home from my last call at night and slump down into my chair by the fire I would like to read my medical journals but often I am too tired to look at anything difficult. I just can't face a lot of long words and long sentences. But perhaps then my wife says: 'Here is a delightful article by Dr. John Stokes, which this afternoon I read and enjoyed and understood.' And then I read it, sitting up long after I should have gone to bed, because it flowed along so easily and interestingly, with here and there a delightful little story to make and hammer home a point. Some long-winded doctors tell me that such writing is not dignified, but all I say is, give me a lot more like it."

Surely physicians who would like to improve the appearance and the reading qualities of their papers would do well to buy this little book and to read it over and over again.

Walter C. Alvarez, Rochester, Minn.

Diagnosis and Non-operative Treatment of the Diseases of the Colon and Rectum. By Schwarz, Gottwald, Goldberger, Jacques and Crocker, Charles. New York, Paul B. Hoeber, Inc., Harper and Brothers, 540 pp., 1937.

THIS book has been written from the point of view that, in the case of proctology, the reader needs not only a good description of disease entities, with details as to symptoms, diagnosis and treatment, but also special instruction in the ways in which the roentgen ray and sigmoidoscope can be used to help in understanding the problem of the particular patient. An effort has been made by the three writers to bring together in this book information available in Austria, Germany and the United States.

The book is interestingly written and well illustrated. There are many colored representations of what can be seen through the sigmoidoscope. As usual with textbooks, the reviewer must feel that in many places the treatment of the subject is inadequate from the point of view of the specialist, but the answer would probably be that specialists never look to textbooks for information. Perhaps they would if writers who were really competent to teach would make their books adequate and up-to-date. Unfortunately they rarely do, and as a result the specialist who looks through a textbook is usually repelled by the number of statements he finds there which are antiquated, inadequate, or positively misleading. On the whole, however, this book will be of considerable assistance to students of proctology. Particularly helpful will be the fine bibliography.

Walter C. Alvarez, Rochester, Minn.

Handbook of Microscopical Technique. By C. E. McClung. New York, Paul B. Hoeber, Inc., Harper and Brothers, 698 pp., 1937.

ONE of the finest things that Paul Hoeber has done through the years is to produce in beautiful format, valuable handbooks on technics of various kinds, each chapter being written by an able specialist in the particular field. This work is a beautiful example of his craft. Dr. McClung has gathered together as contributors such men as Chambers, Cowdry, Downey, Mallory, Penfield and Florence Sabin. All those who work in laboratories are in their debt and will want this book.

Walter C. Alvarez, Rochester, Minn.

Gastroscopy. The Endoscopic Study of Gastric Pathology. By Dr. Rudolf Schindler, University of Chicago Press, Chicago, Illinois, 343 pp., June, 1937.

THE author states that "this book is based on the premise that the functional tests of the stomach used for the last sixty years have failed as methods of diagnosis and that only the morphological methods — X-ray and gastroscopy — are of direct diagnostic value."

The volume contains much information for the gastro-enterologist and particularly for the gastroscopist. No one making gastroscopic studies can afford to be without this book as it explains in detail the methods used by a pioneer in gastroscopy who has

contributed more than anyone to the development of gastroscopic methods. The text is very readable and the colored plates showing the gastroscopic views of various lesions are particularly instructive. Throughout the book the author emphasizes the necessity for roentgenoscopy in association with gastroscopy in the diagnosis of diseases of the stomach and shows that the one method must supplement the other in order to make the examination of the stomach complete. A considerable amount of space is devoted to the classification and diagnosis of gastritis, a lesion which is rarely detected by roentgenoscopy.

Porter P. Vinson, Richmond, Va.

ERRATUM

Apology is made to Dr. C. M. Wilhelmj and the readers for the erroneous inclusion of a chart with his editorial in the August issue. This ought to have been held for use with an article by Dr. Wilhelmj appearing in a later issue.

—Supervising Editor.

EDITOR'S NOTICE

The recent Supplement to the August issue of this Journal was sent out on my own responsibility and without consultation with the Board or Editorial Council. I make this statement for the purpose of completely freeing all editorial members of this Journal from any responsibility in the matter.

Beaumont S. Cornell.

Abstracts

WILLHELMJ, ELLIS W.

Further Observations of the Histidine Treatment of Peptic Ulcer. Annals of Inter. Med., Vol. X, pp. 1365-1370, March, 1937.

Since January, 1935, 42 roentgen-ray proved cases of peptic ulcer have been treated with a series of 24 daily intramuscular injections of 5 c.c. of 4 per cent distidine monohydrochloride. Of these 42 cases, 28 have been followed closely and rechecked clinically and radiographically for at least one year following treatment. The patients were requested to carry on their usual activities of life, were given no medicine whatsoever and advised to eat a general diet. From this group 21 cases were selected as showing uncomplicated peptic ulcer and no other physical ailment.

Of the entire group of 28 cases carefully followed there were 17 males and 11 females, whose ages varied from 20 to 72 years, the average being 45.2 years. A history of typical ulcer symptoms, with intermittency, food and alkali relief and epigastric distress two to four hours after meals, was presented in about 90 per cent of the cases. Four of the patients had had previous hemorrhages. Two cases gave a history of perforation and three cases presented an entirely atypical symptomatology, the diagnosis being established entirely by roentgen-ray findings. The average duration of symptoms was 8.8 years.

Of the 28 cases in the series, 23 were duodenal and five were gastric ulcer. The roentgen-ray findings were rechecked every three months for one year and at the end of this time two cases of the duodenal ulcer group were considered cured. Sixteen of the duodenal cases and five of the gastric cases were unimproved roentgenologically. In percentage 75% of the cases showed no improvement radiographically, while 8.6 per cent were considered cured and 21.7 per cent improved.

The clinical results of the entire series show six cases, or 21.4 per cent received complete and total relief; eleven cases or 39.3 per cent received only partial or no relief; and eleven cases or 39.3 per cent received complete relief but relapsed in the first year following treatment.

In the group of 21 selected cases we find 28.6 per cent of the cases received permanent relief, 23.8 per cent were complete failures, and 47.6 per cent received complete immediate relief with relapse within the first year.

Ten of the patients from the selected group of 21 were given a second course of treatment four to six months after finishing the first course, regardless of whether or not they had relapsed within that period. Those patients who had previously relapsed all again developed symptoms following the second course of treatment.

Willhelmj concludes that this treatment will undoubtedly produce remissions in a fairly high percentage of uncomplicated ulcer patients, 76.2 per cent in the selected series, but the permanent relief is no greater than that derived by various other methods of ulcer treatment and the final results obtained do not justify the routine use of this procedure in the management of peptic ulcer patients.

B. B. Vincent Lyon and
C. W. Wirts, Jr.

JEGHERS, HAROLD.

"Night Blindness as a Criterion of Vitamin A Deficiency: Review of the Literature with Preliminary Observations of the Degree and Prevalence of Vitamin A Deficiency Among Adults in Both Health and Disease." Annals of Int. Med., Vol. X, pp. 1301-1331, March, 1937.

The purpose of this report is to give some observations concerning the degree and prevalence of vitamin A deficiency among a group of supposedly normal adults and also to give some preliminary results obtained by testing persons afflicted with various types of disease.

There is now abundant available evidence to show that in older children and adults, essential hemeralopia (night blindness) is usually the earliest and the most constant manifestation of avitaminosis A, and that it may exist for years without any other sign of the appearance of such a deficiency. This can be tested by at least four suitable methods, but for many years foreign investigators have been using various types of photometers to measure quantitatively minor to moderate degrees of night blindness. The Birch-Hirschfeld photometer was used in this study and the entire procedure for testing one patient takes less than twenty minutes. The author emphasizes that it is important to be sure that no intra-ocular condition is present which can cause night-blindness, before assigning the lowered photometer reading to vitamin A deficiency.

A total of 274 satisfactory photometer tests were performed. The subjects were divided into three groups as follows:

Group 1 consisted of 22 physicians who ate in the doctors' dining room at the Boston City Hospital.

Group 2 consisted of 149 subjects comprising W. P. A. employees, medical students, technicians and graduate nurses.

Group 3 consisted of 103 ambulatory patients. Tests in this group were usually made shortly before discharge.

Group 1 consisted of healthy males varying from 24 to 35 years of age and free of serious intra-ocular disease. This was considered the control group because of excellent cooperation, reliable dietary history and the uniform nature of their diet. The meals contained an abundant and varied supply of vitamin A and carotene. Butter, milk and cream in unlimited amounts were served at every meal; eggs five times a week; cheese once per week; liver once a week; whipped cream on desserts once a week; ice cream three times a week and pigmented (yellow or green) vegetables and fruit daily and often at each meal. With two exceptions the photometer reading of each person in this group fell into a narrow range which was considered normal, the exceptions were due in one instance

to attempted weight reduction and, in the second to many food dislikes.

Members of Group 2 were healthy in the sense that they worked daily and had no specific complaints of disease. Of 149 subjects tested 98 (65.8 per cent) fell into the normal group. Of the remainder, 42 (28.2 per cent) were mildly deficient in vitamin A; seven (4.6 per cent) were severely deficient. The reasons for the deficiencies could usually be assigned to some obvious dietary lack. This arose through the expense of the vitamin A containing foods or peculiarities in food habits (weight reduction, dislikes, etc.).

Group 3 comprised 103 ambulatory patients convalescing from the usual run of diseases which one finds in a general medical ward. No very sick or bedridden patients were tested because the subject had to be well enough to walk to the dark room.

Thirty-four (33 per cent) of those tested showed no deficiency.

Forty-three (41.7 per cent) were found to be mildly deficient in vitamin A; 18 (17.6 per cent) moderately deficient; and eight (7.7 per cent) severely deficient.

The cause of the high deficiency in this group is explained as follows: (1) Persons in this group belong for the most part to the lower economic level. (2) Many had diseases which cause anorexia, vomiting, diarrhea or otherwise hindered the proper ingestion and absorption of the vitamin. (3) Many were entirely ignorant of what constituted an adequate diet. (4) Some had fever, infection or other disturbances which increased the metabolic need for vitamin A. (5) Several had liver damage which prevented the proper storage of vitamin A or conversion of carotene to vitamin A.

Results of Therapy of Vitamin A Deficiency. In the present study 14 of the persons in Group 2, who showed low photometer readings, were treated with vitamin concentrates with no change in their diet. Each person received a daily carotene capsule containing 10,000 U.S.P. units of vitamin A activity. Each person was re-tested at the end of two, three and four weeks after the therapy, with one exception (where it took a month) the photometer reading returned to the normal range after either two or three weeks.

The author also extensively reviews the literature dealing with the physiology, biochemistry, pathology and clinical aspects of vitamin A deficiency.

B. B. Vincent Lyon and
C. W. Wirts, Jr.

SHAY, HARRY AND FIEMAN, PHILIP.

The Galactose Tolerance Test in Jaundice; a Consideration of the Evidence Permitting the Measurement of Galactose Utilization by Urinary Excretion; Some Sources for Error in Its Interpretation; and an Addition in Routine Technic. Annals of Inter- Med., Vol. 10, pp. 1297-1303, March, 1937.

In a study of the metabolism of galactose in the human subject, Shay, Schloss and Bell concluded that this hexose was best suited for testing the carbohydrate function of the liver. The urinary excretion of this sugar, orally administered, acts adequately as a measure of hepatic carbohydrate function because no renal threshold for galactose can be demonstrated, the utilization of galactose by tissues other than the liver is minimal or nil, and the urinary excretion after a standard dose of galactose may be taken as an invariable unit of measure.

The authors adopted the 3 gram level of urinary excretion of galactose as the upper limit of normal, five hours after a 40 gm. dose. They also claim that this test can have no value when applied as a general liver function test, but as an aid in the differential diagnosis of jaundice it is of incalculable value. It has its greatest value if applied early in the course of jaundice, and in the painless jaundice group of middle and later life.

Because of the possibility of some glucose excretion after the dose of galactose in some disturbed endocrine states (thyroid, adrenal, pituitary, potential or mild unrecognized diabetes, or in the case of impaired renal tubular absorption because of so-called low renal threshold) the authors feel that differential fermentation of the urine with properly prepared yeast should be made part of the routine technique in all cases in which the excretion of reducing substances in the five hour urine exceeds a grams.

B. B. Vincent Lyon and
C. W. Wirts, Jr.

FELSON, JOSEPH AND GORENBERG, HAROLD.

Chronic Dysentery, Distal Ileitis and Ulcerative Colitis. A Follow-up of the Jersey City Epidemic of Bacillary Dysentery. Amer. Jour. Med. Sci., Oct., 1936.

A nine to twelve months' follow-up study was made following the major Jersey City epidemic of 1934. Only hospitalized patients were included in the investigation. 122 cases were included. There were persistent or recurrent symptoms and signs in 46 (37.7%). Diarrhea with blood, mucus and pus, 8 (6.5%). Watery diarrhea without gross blood, 12 (9.8%). Bloody evacuations without diarrhea, 3 (2.4%). Miscellaneous intestinal symptoms, 23 (19.0%).

In Table 2 are included visible evidence of ulcerative colitis or ileitis. (a) Roentgenographic evidence of chronic ulcerative colitis, 8 (6.5%). (b) Additional cases with sigmoidoscopic evidence of chronic ulcerative colitis, 2 (1.7%). (c) Chronic distal ileitis (2 at operation, 1 at necropsy*) 3 (2.5%).

Discussion of Statistical Data and Their Significance. Approximately 10% developed chronic distal ileitis or ulcerative colitis by the end of the first year. The initial infection was due to B. dysenteriae (Flexner) in each instance. Although the acute disease subsided, it had never cleared up completely. In a percentage of these chronic cases B. dysenteriae may still be recovered after the lapse of a year or more; in the majority of them this organism cannot be found on repeated fecal cultures. Secondary intramural invasion by the enterococcus and B. coli occurs through the ulcerations originally caused by B. dysenteriae. If chronic distal ileitis and chronic ulcerative colitis are the result of bacillary dysentery, accurate diagnosis, prompt isolation, and adequate treatment are essential.

Antidysentery serum of high antitoxin content must be given within the first 24 to 48 hours to be effective. Foodhandlers should be supervised.

Allen Jones, Buffalo.

MCGEE, LEMUEL C., CONRAD, HAROLD A. AND WILSON, ANGUS K.

Electrocardiographic Changes with Perforated Duodenal Ulcer; a case report. Ann. of Int. Med., Vol. 10, pp. 1222-1226, Feb., 1937.

A case is reported of a 39 year old coal-miner who was admitted to the hospital in shock and semi-coma, who had collapsed in his home 12 hours previously following an attack of severe upper abdominal pain. A tentative diagnosis of either perforated duodenal ulcer or acute pancreatitis was made. An electrocardiogram showed inversion of T-waves in Leads 2 and 3 with elevation of the S-T interval in those Leads as well as in Lead 4. This finding suggested the possibility of coronary occlusion with posterior surface infarction.

The patient recalled that for the previous six months he had had recurring attacks of rather severe epigastric pain with shortness of breath. The periods of distress were too numerous to recount, but the patient was positive in the assertion that the discomfort was related to exertion and that resting a few minutes provided relief. He had stopped work two weeks before because of marked dyspnea and weakness. The patient died after being in the hospital 70 hours.

At autopsy 3 liters of greenish brown fluid were removed from the peritoneal cavity. Abundant purulent exudate and thick fibrin covered the

*Almost entire ileum and all of colon involved.

omentum and bowel. The fundus of the gall bladder covered a perforation in the duodenal wall. The gall bladder itself was intact, but covered with exudate and fibrin. When the duodenum was opened, two typical, chronic "kissing" ulcers were found, the upper one alone having perforated. This ulcer measured about 5 mm. by 6 mm. in diameter. Careful dissection of the coronary vessels of the heart revealed no occlusion, and after extensive sectioning of the myocardium, no infarction, either old or recent, was revealed. Histological study confirmed the gross pathological findings.

Reference is made to the occasional striking association between disease of the gall bladder and symptoms referable to the heart, noted in the past 30 years.

The electrocardiographic changes noted in this report may have resulted from (1) shock and low systemic blood pressure with insufficient oxygenation of the cardiac musculature, (2) embarrassment of circulation due to displacement of the heart by the elevated diaphragm or (3) a reflex change in cardiac circulation and function initiated by inflammatory process about the duodenum and gall bladder.

B. B. Vincent Lyon and
C. W. Wirts, Jr.

MOENCH, L. MARY.

Variations in Response to Therapy in Pernicious Anemia. Ann. of Inter. Med., Vol. 10, pp. 1115-1129, Feb., 1937.

Adequate treatment of pernicious anemia should result in the restoration of a normal blood picture and in a disappearance of those symptoms and signs which are not due to irreversible tissue reactions. This study investigates the amount of potent factors required to bring the erythrocytes to normal and to maintain these cells at such a level if, in spite of apparently adequate therapy, a significant fall in the red blood cell count may occur; and if such a fall occurs whether it is attended by other evidence of clinical relapse.

The total series of patients studied numbered 36; of this total, 33 patients had been given treatment for a sufficient period of time to elevate the red blood cell count to normal, and of these, 32 had been treated in the clinic for periods of time that permit a satisfactory evaluation of data which might yield information about maintenance conditions. Of the group of 32 patients the average length of the maintenance period was 21 months, the shortest period being five and the longest 50 months. The preparations used in treatment were Lederle Liver Extract (3 c.c. of which were derived from 100 grams of liver) and an unconcentrated extract prepared in the laboratories of the New York Hospital (10 c.c. of which were derived from 50 grams of liver). These preparations were given by intra-muscular injection, the average amount consisting of a total monthly dose of material derived from 300 grams (Lederle) or from 200 grams (New York Hospital). The patients were seen in the clinic at least once a month when counts were made and the patients questioned and examined. When the red blood cell count fell appreciably or the patient showed some evidence of relapse the amount of material was increased or was supplemented by whole liver or by Lextron.

In this series of pernicious anemia patients who were in remission the average count for the entire group of women (19) was 4.5 and for men (13) 4.83. These averages are lowered by 10 (5 men and 5 women) of the cases not satisfactorily controlled; 70% of the series gave a satisfactory hematologic response. Of these 10 patients whose erythrocyte counts did not measure up to the normal standard with therapy, which is usually adequate, eight have been apparently fully controlled as far as symptoms and signs are concerned. In two, the disease showed some evidence of activity. All of the women and three of the men in this group received approximately twice the average amount of liver given to 70 per cent of the original group of patients.

Of the 33 cases, 15 reached the 4.5 million level in two months or less. The average total amount of liver extract given was that derived from 670 grams (combined New York Hospital and Lederle Extracts). The average initial count was 2.6 millions erythrocytes. The duration of symptoms prior to treatment averages 13.1 months. Of a second group requiring more than two but under three months to reach this level, there were 11 patients with an average initial count of 1.9 million. The average amount of material used was derived from 1072 grams (combined extracts). The approximate duration of symptoms averaged 23.1 months. A third group (7 patients) required more than 3 months for erythrocyte count to reach the 4.5 million level, and to whom a minimum of 1600 grams and a maximum of 6,600 grams of liver were given. The initial count in these patients was 2.9 million.

Of the total series of 36 patients only eight had never experienced symptoms of peripheral or central nervous system involvement. Following treatment of 28 who experienced symptoms, 4 were entirely relieved, 15 were improved, in 5 there was no change and in 3 they became worse. In 1 the result was indeterminate.

It must, therefore, be concluded that each patient with pernicious anemia must be managed as a separate problem and the dose of liver individualized on the basis of the trend of the erythrocyte count averaged over stated intervals of time. No unqualified prediction can be made as to the length of time necessary to bring the count to normal on the basis of the initial count or as estimated by the response of the average patient, and although the majority of patients are benefitted by treatment, no absolute prediction, as to relief of symptoms, can be made.

B. B. Vincent Lyon and
C. W. Wirts, Jr.

FREUND, HUGO A.

Clinical Manifestations and Studies in Parenchymatous Hepatitis. Ann. of Inter. Med., Vol. 10, pp. 1144-1155, Feb., 1937.

A study is presented of the effects of a chemical compound on two men exposed to the vapor of a nitrosamine. These two patients, chemists, while engaged in the manufacture of dimethylnitrosamine, inhaled this chemical poison in sufficient amounts to produce headache, backache, abdominal cramps, nausea, anorexia, weakness, drowsiness and giddiness.

CASE REPORTS

Case 1. T. C., chemist, age 29, single. Chief complaints are pain in the upper right quadrant, nausea, a sensation of weakness in the upper abdomen and occasional abdominal cramps. He dates the beginning of his illness about July, 1933, while engaged in the above mentioned work. August 16 he noticed his abdomen was distended. In the hospital about two and one-half quarts of fluid were withdrawn by paracentesis. Although the abdomen slowly filled again no further tapping was performed. After spending three months in a tuberculous sanitarium and a similar period in bed at home, and a period for thorough examination in New York City, he was advised to return home with instructions to rest during the summer of 1934. Gradually the attacks of pain became less frequent. The patient states he was jaundiced at the beginning of his illness and for a short period in January, 1935. He admits that the entire illness has made him somewhat nervous and depressed. There is no history of clay colored stools, nor dark urine. His habits are good as to alcohol, smoking and eating. There is no family history of tuberculosis or cirrhosis; both parents and brothers are living and well. On physical examination there is tenderness throughout the whole abdomen on light palpation, especially in the upper right quadrant where there is definite muscle spasm. The liver is felt two fingers breadths below the costal margin and is moderately firm and tender. The spleen is not palpable. All reflexes and tests of sensation are

normal. The non-protein nitrogen is 40 mg. per cent, blood sugar 66 mg. per cent and the Kahn test is negative.

On February 17, 1936, the blood count showed: Hgb. 84 per cent. Erythrocytes 3,680,000. Leukocytes 7,000. Color Index 1.1. Reticulocytes 1 per cent. Thrombocytes 349,400. Differential Count: Metamyelocytes 3 per cent; neutrophiles, stab. 20 per cent; neutrophiles, segmenters 26 per cent; eosinophiles 0; basophiles 1 per cent; total of granulocytes 50 per cent; lymphocytes 48 per cent; monocytes 2 per cent. The urinalysis phenolsulphonephthalein test, blood chemistry, sugar tolerance and van den Bergh tests showed nothing unusual. The Bromsulphalein, basal metabolic rate, gastro-intestinal roentgenogram and cholecystograms revealed no abnormal findings. The pulse averaged 80 and the temperature was not elevated during hospitalization.

Case 2. H. B., 26, white, single, chemist. This patient filled the position of the patient just described when the latter was compelled to stop working because of his illness. On November 18, 1934, he began symptoms similar in type and onset to the first patient.

On December 26, 1934, he entered the hospital acutely ill. The sclerae were slightly icteric; there was free fluid in both pleural cavities. The abdomen was distended and contained fluid, but was not rigid. The liver was felt three fingers below the right costal margin. Ascitical fluid ranging from 3,500 c.c. to 6,000 c.c. was removed by parencentesis on seberal occasions. Laboratory findings: Urinalysis negative. Blood count (Jan. 24): Hgb. 80 per cent; erythrocytes 4,600,000; leukocytes 9,900; polynuclears 72 per cent; small lymphocytes 28 per cent; some variation in the size and shape of the red blood cells was noted. Blood Chemistry (Dec. 28, 1934): Icteric Index 16; van den Bergh reaction, faintly positive, direct and indirect; Kahn negative. Roentgenogram of chest showed pneumonitis in the right base. An exploratory laparotomy showed a large amount of yellowish ascitic fluid. Liver extremely engorged, about a hand's breadth below margin of rib, smooth and purplish in color. Spleen markedly engorged and lobulated, purplish in color. Gall bladder and duct somewhat thickened; no stones; emptied readily. The patient died on January 28, 1935. Autopsy: The outstanding findings were 400 c.c. of fluid in the right pleural cavity and about 100 c.c. of blood stained serous fluid in the left. The spleen weighed 320 gms. and was uniformly mushy in consistence. The biliary channels were patent. The liver weighed 1380 grams, was dark greenish, mottled brown and rather firm in consistence. On section it was of similar appearance.

Summary of microscopic findings: Liver: Acute diffuse degeneration of the whole parenchyma with focal and diffuse areas of necrosis. The necrotic areas are infiltrated with round cells and phagocytes. Multiple periportal miliary hemorrhages. Areas of intense regenerative proliferation of liver cells with marked irregularity in size and staining reaction of protoplasm and nuclei.

Some experiments were performed permitting mice and dogs to inhale dimethylnitrosamine and autopsy showed microscopical changes in the livers similar to that found in Case 2.

The selective toxicity of the chemical dimethylnitrosamine appears to be adequately demonstrated in this paper.

B. B. Vincent Lyon and
C. W. Wirts, Jr.

RENANDER, AXEL.

(Benign Gastric Tumors) Gutartige Magentumoren. Acta Radiological, 17:491. Oct. 31, 1936.

The author describes two cases of benign tumor of the stomach, one a plum-sized neurofibroma and the other an orange-sized lipoma with a thumb-sized ulcerous crater. Roentgenological diagnosis of benign gastric tumor was made possible by the uniformly rounded appearance of these growths on the roentgenograms as well as the plasticity of the mucous membrane relief around the one tumor and the unaltered appearance of the other tumor at the control examination.

James T. Case.

ROTHMAN, MAURICE M., MERANZE, DAVID R. AND MERANZE, THEODORE.

Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice. Amer. Jour. Med. Sci., p. 526, Oct., 1936.

Phosphatase is apparently concerned with the metabolism of bone, and is found in bone, liver, kidney, intestinal mucosa, blood, bile and feces. As studied in the blood, the serum and plasma phosphatase have been found moderately increased in local bone atrophy, generalized osteoporosis and osteomalacia. In hyperparathyroidism, the findings are 4 to 5 times the normal, and in active infantile rickets, 10 to 13 times above the normal.

Roberts found high values in jaundice. He noted a difference in the phosphatase content of the plasma as between cases of obstructive and non-obstructive jaundice. He studied the phosphatase values in 52 cases of jaundice, 21 obstructive; 31 non-obstructive. The authors cite his conclusion that by means of the phosphatase level of the blood, toxic infections and catarrhal jaundice may be distinguished from that of the obstructive type. The phosphatase values were normal in 5 cases of hemolytic jaundice. The writers cite the observations of many workers, and note the divergence of opinions and conclusions in the matter, some affirming and some denying that the test was of value in the differential diagnosis of jaundice.

Important experiments were conducted by ligation of the common duct in dogs. The writers believe, however, that the phosphatase is valuable. The method employed was as follows: Fasting blood was used. 2 c.c. of plasma (citrated blood) is mixed with 2.3 c.c. of distilled water and 0.7 c.c. of N/10 sodium hydroxid. This produces a pH of approximately 8.9. To this is added 1 c.c. of a 1% solution of sodium betaglycerophosphate. The mixture is then incubated at 37.5° C. for 2 hours, after which its inorganic phosphorus content is determined by the method of Fiske and Subbarow. At the same time, the initial inorganic phosphorus content of the plasma is determined, using another 2 c.c. of the original blood. Both of these values are determined in mgm. per 100 c.c. of blood plasma. The difference of these two values represents the number of mgms. of inorganic phosphorus liberated by the enzyme, phosphatase, from the substrate under the above conditions. Each mgm. thus obtained is expressed as units of phosphatase per 100 c.c. of blood plasma.

Phosphatase values in cases without jaundice or liver disease were found for adults less than 6 units, and for children less than 15 units. In obstructive jaundice, high phosphatase values were found. In cases of non-obstructive jaundice, the authors studies led them to agree with Roberts; that is, in cases of jaundice phosphatase values up to 10 units indicate that the jaundice is non-obstructive in etiology, and values above 10 units indicate an obstructive mechanism.

Allen A. Jones, Buffalo.

FRIEDENWALD, JULIUS AND MORRISON, SAMUEL.

Use of Gastric Antacids. J. A. M. A., Vol. 108, pp. 879-885, 1937.

Antacids are used to reduce or neutralize the acidity of the gastric secretion preferably by local action rather than through systemic effects. Sodium bicarbonate and magnesium oxide are thought to be among the most powerful stimulants of gastric secretion. This is because they render the contents of the stomach alkaline, which condition stimulates the secretion of acid.

Sippy, in the treatment of ulcer, attempts to bring about complete neutralization of the gastric contents. Some clinicians while agreeing that removing the irritation of the gastric acid by alkalies is rational treatment, also believe that the amount of alkali administered by the Sippy method is too great. Because of this the Sippy

powders have been altered so that number two contains 0.65 gms. of calcium carbonate and 0.65 gms. of Heavy Magnesium Oxide. If diarrhea occurs Bismuth Subcarbonate may be used to replace the heavy magnesium oxide or powder one substituted for powder two.

Winkelstein tries to avoid the high night acidity curves by using a continuous milk drip containing five gms. of sodium bicarbonate to the quart, regulated so that the patient receives three liters per day. Wasika and Emery have found an alkalinized powdered milk preparation administered every hour to be better than the Sippy regimen.

Hurst uses milk containing 0.65 gms. of sodium citrate with magnesia magna per glass because in addition to their being proficient alkalies the sodium citrate combines with the calcium of the milk and prevents the renin from acting on the caseinogen, thus preventing the formation of irritating curds. His second mixture contains 0.3 mgs. of atropine sulfate and is administered twice daily at eight a. m. and three p. m. Magnesia magma is given to regulate bowel evacuation. Heartburn is treated by giving .4 gms. of prepared chalk between feedings. He also prescribes 15 gms. of powdered charcoal with water at seven a. m.

In treating peptic ulcer alkaline therapy of some kind is indicated. However, many clinicians believe that large doses are harmful and Crohn has shown that neutrality exists only for a short time and it is followed by a hypersecretion of gastric acids. Because of this the tribasic phosphate of calcium and magnesium have been recommended. These salts act locally and not systemically and therefore can be given continuously without toxic effects.

The effect of alkalies is to increase the circulation to the stomach by a slight irritant action, to render mucus less tenacious, and to render the contents of the stomach neutral or alkaline. Antacids are therefore indicated in gastric hyperacidity, in peptic ulcer, in chronic alcoholic gastritis, catarrhal duodenitis and in the neuroses. They should be given either dissolved in water or mixed in it if insoluble one or two hours after meals. The antacids generally used are aluminum silicate and aluminum hydroxide, the basic phosphates, bismuth subcarbonate, sodium and potassium bicarbonate, magnesium salts and calcium salts.

Alkalosis may develop especially when sodium bicarbonate is used over a long period of time. This is very likely to occur in those patients who have a chronic nephritis, pyelonephritis, hepatic cirrhosis, arteriosclerosis or hypertension. It is manifested by such symptoms as headache, drowsiness, anorexia, nausea, vomiting, muscle ache, nervousness, mental depression, vertigo and aching pain in the muscles and joints. In addition, other complications may arise such as the formation of a gastrolith of magnesium and sodium, interference with digestion, and catarrhal gastritis due to a reflex hypersecretion of acid.

Francis D. Murphy, Milwaukee.

ELIASON, ELDRIDGE L. AND ERB, WILLIAM H.

Rectal Prolapse. Ann. of Surg., 105:2, 199-202, Feb., 1937.

The rediscovery in 1925 of the elastic ligature method of treatment of rectal prolapse is the basis for a discussion of the method and the report of three cases.

Weinlechner first treated rectal prolapse by this method in 1883 but it was practically abandoned with the advent of aseptic surgery. The method was discouraging also because of the accompanying pain, urinary retention, and difficulty in expelling gas. The method consisted of the slow amputation of the prolapse by placing a rubber tube into it and tieing an elastic ligature around it.

Kleebarg used the elastic ligature in 1879 only as a means of controlling bleeding while amputating and suturing the rectum. Mikulicz in 1889 popularized the amputation operation and reported seven cases with no mortality. In 1907 Lenormont stated there was a 10% danger of peritonitis.

There have been four cases reported by Reid since his rediscovery of the method in 1925, one by Wangensteen and three by the authors. None of the above unpleasant symptoms was present in these cases. The first case in the authors series was complicated by hemorrhage while attempting to remove the slough and stricture due to lack of close follow up care.

The authors place a thick, stiff, three-quarter inch rubber tube in the rectum, pull the prolapsed portion over it, tie a heavy rubber band around the bowel close to the mucocutaneous junction, and suture the prolapsed portion to the tube to prevent retraction.

This method is believed to be of value in certain cases but not in all. Prolapse in children especially, which make up about 70% of cases, should be treated more conservatively. The strongest indication is irreducible prolapse with infection of the prolapsed portion. There are no reports of recurrence in the literature compared with 6% to 15% with other methods. Close postoperative observation will prevent the main danger, stricture, and hemorrhage will probably not occur if the slough is allowed to separate spontaneously. Slight relaxation of the anal sphincter was noted in one patient 22 days following operation.

Wayne W. Flora, Chicago.

Note: This procedure is a step backward rather than an advance. Obstruction may ensue if the small intestine lies between the walls of prolapsed rectum, anteriorly. It is preferable to determine by direct inspection through the incised rectum whether the small intestine is down and if it is to adequately replace it. To depend upon necrosis in an infected field denies a general surgical principle. Hemostasis is more certain with ligature.

HURST, ARTHUR F. AND KNOTT, F. A.

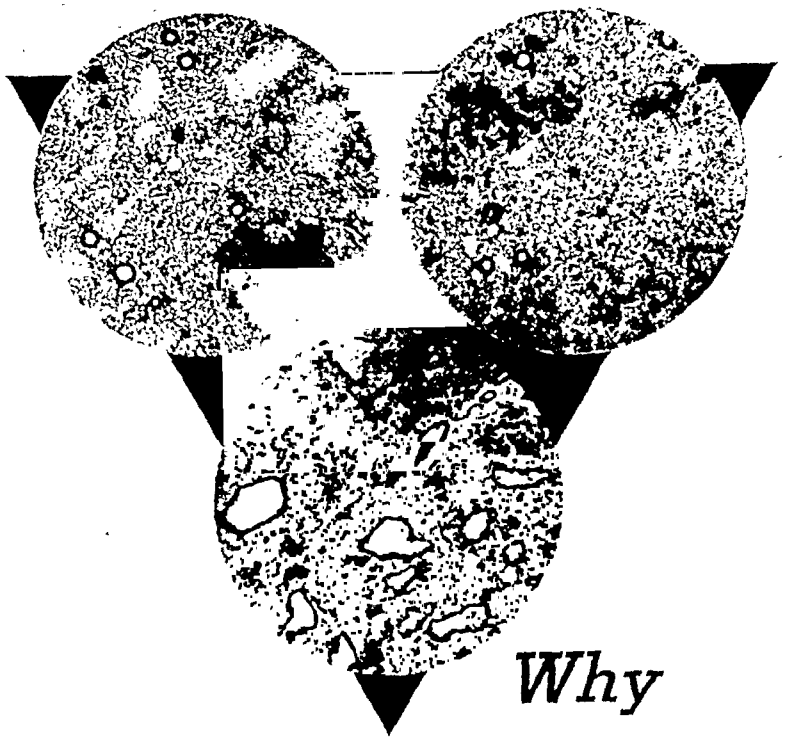
British Dysenteric Infections. The Lancet, p. 1197, Nov. 21, 1936.

Bacillary dysentery has been endemic in Great Britain since the fourteenth century and the mild and scattered epidemics of today are the direct descendants of the serious and widespread epidemics of the seventeenth and eighteenth centuries, reinforced by infection brought home by soldiers from the Crimean and South African Wars and the Great War.

Attention has recently been drawn to the possible spread of bacillary dysentery in England as a result of the increasing popularity of pleasure cruising creating a source of infection by taking on food at ports of call where dysentery is common.

Modern bacteriological investigations and the clinical records of the past indicate that the dysentery of Great Britain must always have been predominantly of the Flexner and allied Sonne types, although the occurrence in earlier days of occasional outbreaks of high mortality makes it probable that Shiga infections were not quite as uncommon as now. More recently the majority of cases in Great Britain, sufficiently severe to deserve clinical description as dysentery, are also Flexner infections. A few are caused by bacilli of the Schmitz (atypical Shiga) type, and a small proportion of the comparatively common Sonne (atypical Flexner) type give rise to true dysentery. Shiga dysentery is almost unknown. However, numerous epidemics of mild diarrhea are caused by infection with Sonne's dysenteric bacillus, which is isolated from the stools in these cases, although clinically they may bear no resemblance to classical dysentery, or bloody flux.

Ulcerative Colitis and Bacillary Dysentery: Ulcerative colitis is probably a sequel of an acute or subacute infective colitis. In many cases a dysentery bacillus is the original infective agent. However, if the bacteriological evidence is taken into account, it suggests that if chronic ulcerative colitis arises from infection with Flexner dysentery bacillus, the infection must generally play no more than the initial part of damaging and lowering the natural resistance of the intestinal mucosa. In a few cases the Flexner infection may persist and these cases are



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examples of true chronic dysentery. But in the majority the Flexner bacilli die out completely and other damaging influences, often secondary infections, affect the colon, producing the characteristic chronic disease with its great tendency to relapse. It is in these cases, too, that the specific agglutinins usually disappear from the blood. In this way the apparently contradictory bacteriological findings can be explained.

This paper, like all of Hurst's and his collaborators' papers, is an excellent study of the subject and should merit careful reading by all doctors interested in gastro-enterology. The subjects are so thoroughly discussed as to make a brief review of each paper quite inadequate.

B. B. Vincent Lyon and
C. W. Wirts, Philadelphia.

HURST, ARTHUR F. AND RYLE, J. A.

The Incidence, Mortality and Treatment of Hemorrhage in Gastric and Duodenal Ulcer. The Lancet, p. 1, Jan. 2, 1937.

In a given case of sudden gastric or duodenal hemorrhage, having excluded such other causes as hepatic cirrhosis, splenic anemia, cancer and the hemorrhagic diathesis, we are usually entitled to make a diagnosis of peptic ulcer, the commonest cause of bleeding from these sites.

Incidence of Hemorrhage in Chronic Ulcer: A full history was obtained from all 586 cases of ulcer investigated in New Lodge Clinic between February, 1921, and February, 1936, and from 751 cases seen in private practice by J. A. R. from 1920 and 1935. The incidence of hemorrhage is about 30 per cent in gastric and duodenal ulcer and 45 per cent in anastomotic ulcer.

Mortality of Hemorrhage from Ulcer: Of 677 patients with hematemesis and melaena from ulcer seen in general practice only nine have died, giving a mortality of 1.31 per cent.

From 1919 to 1935 inclusive, there were 371 cases of chronic gastric, duodenal and anastomotic ulcer admitted to the wards at Guy's Hospital. Of these, 82 or 22 per cent had bled within 48 hours of admission; in 32 of the 82, or 39 per cent, there was a history of an earlier hemorrhage. In 106 of the total 371, or 29 per cent, a previous hemorrhage was recalled. Of the 82 cases admitted for hemorrhage, 54 had gastric ulcers (66 per cent), 22 duodenal ulcers (26 per cent) and 6 anastomotic ulcer (8 per cent). As there were 191 gastric ulcers, 167 duodenal ulcers and 10 gastrojejunal ulcers in the series, the proportion of cases admitted for hemorrhage in gastric ulcer was 27 per cent, in duodenal ulcer 13 per cent and in anastomotic ulcer 60 per cent. The mortality of these cases of ulcer admitted into Guy's Hospital under A. F. H. an account of hemorrhage was 4.8 per cent. The mortality from hemorrhage in patients with a history of previous hemorrhage from ulcer or admitted for ulcer was under 2.5 per cent, and mortality from all cases of ulcer, including those which had never bled was about 1 per cent. Comparing these figures with a private series (J. A. R.) there was a mortality of 3.1 per cent from hemorrhage in cases of severe hemorrhage and a mortality of 0.5 per cent from hemorrhage in all cases of ulcer. In general practice the mortality among patients with hemorrhage from an ulcer appears to be about 1.5 per cent. The authors feel this latter figure to be the nearest possible approach to the natural mortality. If the incidence of hemorrhage in cases of ulcer, whether they have previously bled or not, is only about 0.4 per cent.

Surgery for Hemorrhage from Ulcer (A.F.H.): There have been 586 cases of ulcer (110 gastric, 379 duodenal and 97 anastomotic) in New Lodge Clinic between February, 1921, and February, 1936, and in 3 of these, all duodenal and all operated on while bleeding, the patients have died from hemorrhage. While surgery may frequently achieve success in skillful hands, it can only in very exceptional circumstances be re-

Synopsis of
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By JOHN L. KANTOR, Ph.D., M.D., Associate in Medicine, Columbia University; Gastroenterologist and Associate Roentgenologist, Montefiore Hospital for Chronic Diseases, New York. 302 pages, 40 illustrations. Price $3.50.

This book presents simply, clearly, and concisely, the essential facts concerning the diseases of digestion. An effort has been made to preserve the proper balance between stress and subordination, inclusion and omission, and to emphasize throughout, the ways in which gastroenterology fits into the larger field of internal medicine. To this end the opening chapter on classification has been designed for early orientation, clinical syndromes common to many diseases have been elaborated as fully as possible, and a final section has been devoted to digestion symptoms in extradigestive diseases.

Contents—PART I—GENERAL CONSIDERATIONS. Classification of Digestive Diseases. Diagnostic Methods: History and Physical Examination. Special Tests. Therapeutic Methods. Organic Constitutional Inferiority. The Anomalies. Functional Constitutional Inferiority: The Neuroses. Gastrointestinal Allergy and Food Sensitiveness. PART II—DISEASES OF THE DIGESTIVE ORGANS. Diseases of the Mouth, Esophagus, Stomach, Duodenum, Jejunum and Ileum, Colon, Appendix, Rectum and Anus, Liver, Gall Bladder and Bile Ducts, and Pancreas. PART III—DISEASES DUE TO INTESTINAL PARASITES. The Protozoa. The Flatworms: Cestodes. Trematodes. The Roundworms. PART IV—DIGESTIVE SYMPTOMS IN EXTRADIGESTIVE DISEASES. Nervous, Cardiovascular and Respiratory Diseases. Diseases of the Blood, Metabolism, and the Genitourinary System; Plumbism.

Synopsis of
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garded as judicious. In less experienced hands, the authors fear that it will immediately increase the mortality from this accident.

General Treatment: When local conditions are favorable treatment should be carried out without transportation of the patient. In all cases a quarter of a grain of morphia should be given at once hypodermically and repeated in accordance with the needs of the case, during the first 24-48 hours. All mouth feeding should be forbidden for 24 or 48 hours and in rare cases for 72 hours. A closer study of the advantages of earlier and more liberal mouth-feeding in severe hemorrhage is needed. The mouth may be rinsed but at first not even water should be swallowed. Normal saline, one-half to three-quarters of a pint, slowly administered by rectum, should be given four-hourly. The latter usually controls constipation about the third day. Injection of proprietary hemoplastic sera is of no value. The hygiene of the mouth must be carefully watched because of the risk of parotitis. When the anxious, earlier phase has passed, medical treatment as for uncomplicated ulcer is gradually instituted. X-ray and other investigations should not be done for three or four weeks.

Transfusion: The authors are inclined to think that transfusion is not without danger and apart from its use as a preliminary to surgery should in general not be given unless the hemoglobin percentage is under 30, and the patient appears to be in danger of death from anemia. About ten ounces is sufficient and transfusion should not be repeated unles hemorrhage recurs.

Iron: Large doses of iron and ammonium citrate (gr. XXX three times a day) can be given safely from the third day following a hemorrhage; they lead to a rapid return of hemoglobin to a normal level and in this way greatly hasten convalescence.

B. B. Vincent Lyon and
C. W. Wirts, Philadelphia.

HURST, ARTHUR F.

Diseases of the Alimentary Canal. The Practitioner, Special Number, Vol. CXXXVII, pp. 409-422, Oct., 1936.

Gastroscopy: Much, possibly too much, has been claimed for gastroscopy as an aid in diagnosis. With its limitations and advantages viewed in their true perspective there can be no doubt that the invention of the flexible gastroscope has added a useful method of gastric investigation. In the detection of chronic gastritis and acute and chronic gastrojejunal ulcers, gastroscopy has proven itself particularly useful.

Treatment of Gastric Duodenal and Anastomotic Ulcer: Hurst cites the over-alkalinization in the treatment of peptic ulcer; the symptoms may be those of uremia and the possibility of alkali poisoning should be remembered whenever a patient who has not hitherto known to be suffering from renal disease develops uraemic symptoms with high blood urea.

Magnesium Trisilicate: Much has shown that this drug absorbs hydrochloric acid without acting as an alkali and can therefore be given in large doses without causing alkalosis. For some months Hurst has given this preparation in thirty grain doses to ulcer patients and alkalosis has never developed.

Histidine: Although there is no doubt that histidine sometimes hastens the healing of an ulcer, especially one of recent origin, Hurst has never seen the slightest benefit result from its use when he tried it in cases in which improvement was slow with the usual treatment. Sandweiss has described some control experiments in the treatment of ulcer with daily injections of 5 c.c. distilled water. Of twenty patients treated the results compared favorably with those obtained with histidine injections, as twelve or 60 per



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cent became symptom free, compared with 55 per cent of the forty patients treated with histidine. Hurst concludes that the use of histidine as a substitute for the proper treatment of peptic ulcer is unjustifiable.

Jejunal and Gastric Feeding by Tube: A comparison of the two methods of continuous drip feeding in ulcer cases, one into the jejunum (Einhorn) and one into the stomach (Winkelstein) showed the latter maintained complete achlorhydria day and night, while in the former there is a continuous secretion of acid juice into the stomach. Hurst believes the method of Winkelstein is worthy of trial in ulcer cases which do not respond to ordinary treatment.

Gastrectomy: In Hurst's cases in which gastrectomy had been performed for gastric ulcer, five out of five showed free acid still being secreted; for duodenal and anastomotic ulcer, five out of eleven showed free acid. Out of thirteen of his private patients in which a partial gastrectomy was performed for anastomotic ulcer, two died from the operation, one developed a new ulcer immediately after the operation and died after a further portion of the stomach was removed a month later; a fourth died from hematemesis without premonitory symptoms two years after the gastrectomy. Exactly one-quarter of the survivors from partial gastrectomy for duodenal or anastomotic ulcer are now suffering from recurrence of symptoms. Hurst has also had one patient with a large anastomotic ulcer and three with severe recurrent hemorrhage following partial gastrectomy performed elsewhere. In view of the unsatisfactory results of gastrectomy, Hurst is now convinced that gastrojejunostomy is the best operation for the exceptional cases of duodenal ulcer in which prolonged medical treatment fails and that anastomotic ulcers should be excised and the parts restored to their original anatomy, unless pyloric or duodenal obstruction is present, when partial gastrectomy must be performed in spite of its dangers.

Regional Ileitis (Crohn's Disease): Hurst has seen two typical cases of regional ileitis and feels that the disease is only just becoming recognized in England, but with the exception of Holland it remains unrecognized in other parts of the Continent.

B. B. Vincent Lyon and
C. W. Wirts, Philadelphia.

CAFFRITZ, EDWARD A.

Nondrainage of the Peritoneal Cavity in Appendiceal Peritonitis. J. A. M. A., 108:1315-1317, April 17, 1937.

Drainage or nondrainage of the peritoneal cavity in peritonitis has lately been the subject of much debate and study. Some surgeons believe that drainage should always be done and some that it should never be done. Others are of the opinion that the procedure should be subject to the surgeon's own discretion.

The author has in the past few years treated twenty-five cases of appendiceal peritonitis by the nondrainage method with very gratifying results. He believes that drainage should be instituted only in those cases in which the primary focus of infection cannot be removed, in cases in which a large amount of necrotic and contaminated tissue is left in the abdominal cavity and in cases of walled-off abscess.

In all other cases he believes drainage is contraindicated. The advantages of nondrainage according to the author are:

(1) There is less morbidity and mortality.

(2) It minimizes the possibility of postoperative mechanical ileus.

(3) It shortens the duration of the illness.

(4) It excludes the possibility of the development of a fistula.

(5) It minimizes the tendency to postoperative hernia.

(6) It minimizes the tendency to postoperative adhesions.

Francis D. Murphy, Milwaukee.

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DAVISON, C. AND STONE, L.

Lesions of the Nervous System of the Rat in Vitamin B Deficiency. Arch. of Pathology, 23:2, 207, Feb., 1937.

Because of the fact that the clinical syndromes, and especially the neuroanatomic lesions induced by the administration of diets deficient in the vitamin B complex to animals are apparently not constant, the authors undertook an experimental study of vitamin B deficiency in the rat. The study included (1) total and subtotal B_1 deficiency; (2) total and subtotal B_1 and B_2 deficiency; (3) controls fed with (a) stock diets, and (b) artificial diets including adequate vitamin rations, and (4) controls subjected to (a) starvation and (b) starvation despite adequate vitamin rations.

In their experiments vacuolation, liquefaction necrosis and chromatolysis of ganglion cells in the mesencephalon, metencephalon and spinal cord, as well as disintegration of the myelin sheaths of the peripheral nerves, were found alike in the animals subjected to diets deficient in vitamin B_1, in both vitamins B_1 and B_2 and in those suffering from pure inanition. Neurologic symptoms such as ataxia, dragging of the legs, convulsions, priapism and retraction of the head occurred in each group. The question of the relationship between these symptoms and the histological changes described was not easily answered. The paralysis might be ascribed to the peripheral neuritis. The convulsions and the tonic retractions of the head might be attributed to the hemorrhages and nerve cell changes in the mesencephalon and metencephalon, and the ataxia and weakness to the starvation. It was believed that the ganglion cell changes of which vacuolation was the most prominent, represented a true pathologic state. The histological changes in animals suffering from inaniton were essentially the same as those in animals deprived of B_1 or both B_1 and B_2. The changes in the peripheral nerves, however, seemed to be most marked in animals subjected only to starvation. It mattered not whether abundant vitamins were given during starvation or not. The clinical symptoms in animals subjected to inanition, however, were not wholly identical with those in animals suffering from vitamin B deficiency, possibly because of the rapid death of the starved animals.

N. W. Jones, Portland.

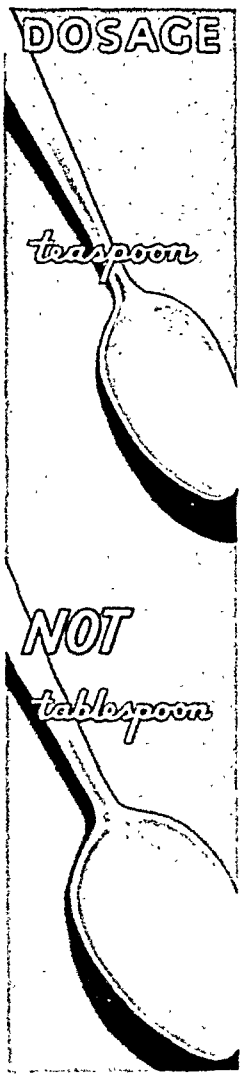
BAKER, A. B. AND LUFKIN, N. H.

Cerebral Lesions in Hypoglycemia. Arch of Pathology, 23:2, 190, Feb., 1937.

From a detailed study of the cerebral changes in three cases of hypoglycemia numerous new and old hemorrhages were found scattered irregularly throughout each brain. These hemorrhages seemed to be most numerous in the brains of the patients who had had the most severe convulsive seizures. Certain histological changes were noted also in the ganglion cells.

In recent years reports of many patients having varied neurological symptoms believed to be related to an accompanying hypoglycemia have been made, and some animal experiments recorded. These reports failed to reveal consistent lesions. The findings in both human and animal material varied from apparently normal conditions to most extensive changes in the cells, nerve fibres and vessels.

The authors also studied the effect of severe hypoglycemic convulsions in rabbits experimentally produced by the injection of insulin. The convulsions were produced once or twice per week over a period of six to eight weeks and each convulsion allowed to continue a varying length of time up to one hour, and then stopped with intravenous injections of 50 per cent dextrose solution. The convulsions were severe but



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the rabbits seemed to recover promptly on the administration of the dextrose. The brains of these rabbits showed no cell alterations of pathologic significance and only an occasional hemorrhage into the brain or meninges.

The authors concluded from this study of both human and rabbit material that the ganglion cell changes in the brains were due entirely to postmortem alterations. They explained the presence of severe and varied symptoms during life and the minimal histological changes found after death on the assumption that the function of the nerve cells may be seriously depressed by the lowered blood sugar and result in varied symptoms without death of the cells, and with a return of normal blood sugar the cells may be able to regain promptly their normal function once more.

N. W. Jones, Portland.

NICKERSON, D. A. AND WILLIAMS, R. H. *Malignant Tumors of the Small Intestine. Amer. Jour. Path., XIII:1, 55, Jan., 1937.*

The authors report 10 cases of primary neoplasm of the small intestine occuring in 11,206 autopsies performed in the Mallory Institute of Pathology during the past 40 years, and review briefly the literature on the subject. The 10 cases consisted of 2 leiomyosarcomas arising in the duodenum and 8 carcinomas, 6 of which occurred in the duodenum and 2 in the jejunum. The incidence of the latter to carcinoma of the intestinal canal in the series was 2.33 per cent.

Metastases, especially into the liver and the regional lymph nodes, occurred abundantly in 7 of the 8 cases of carcinoma. The 2 cases of sarcoma showed no secondary growths.

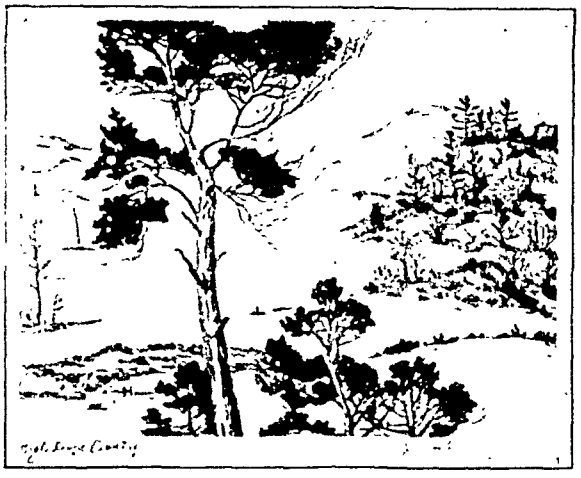
The symptoms and clinical findings are briefly summarized in the report and are of interest. Duration of symptoms before the patients entered the hospital was over 7 months. The clinical picture depended upon the site of the tumor, the type and grade and the presence of metastases. Bloating and epigastric pain after eating, sometimes vomiting or an acute attack of intestinal obstruction occurred. Weakness, loss of weight and strength, altered bowel function and progressive anemia were usually present. The roentgen ray findings in 4 of the 10 cases were dilatation of the stomach with gastric residue without demonstrable gastric lesions and distortion of the duodenum. All were diagnosed as extrinsic tumors or deformities due to adhesions.

N. W. Jones, Portland.

MCCARTY, CLAUDE E. *Sympathectomy for Hirschsprung's Disease and Polyposis. Am. Jour. Surg., 36:2, 531-2, May, 1937.*

A nine year old girl had not had a spontaneous bowel movement since birth and there had been periods of complete obstipation. The presacral nerve, the branches from the third and fourth lumbar ganglia, the lateral roots, and the two principal roots of the inferior mesenteric plexus were divided. The second day following operation the bowels moved naturally. One month later the child was having three normal bowel movements daily. The months after operation there were two stools daily and at the end of a year the bowel movements remained two daily.

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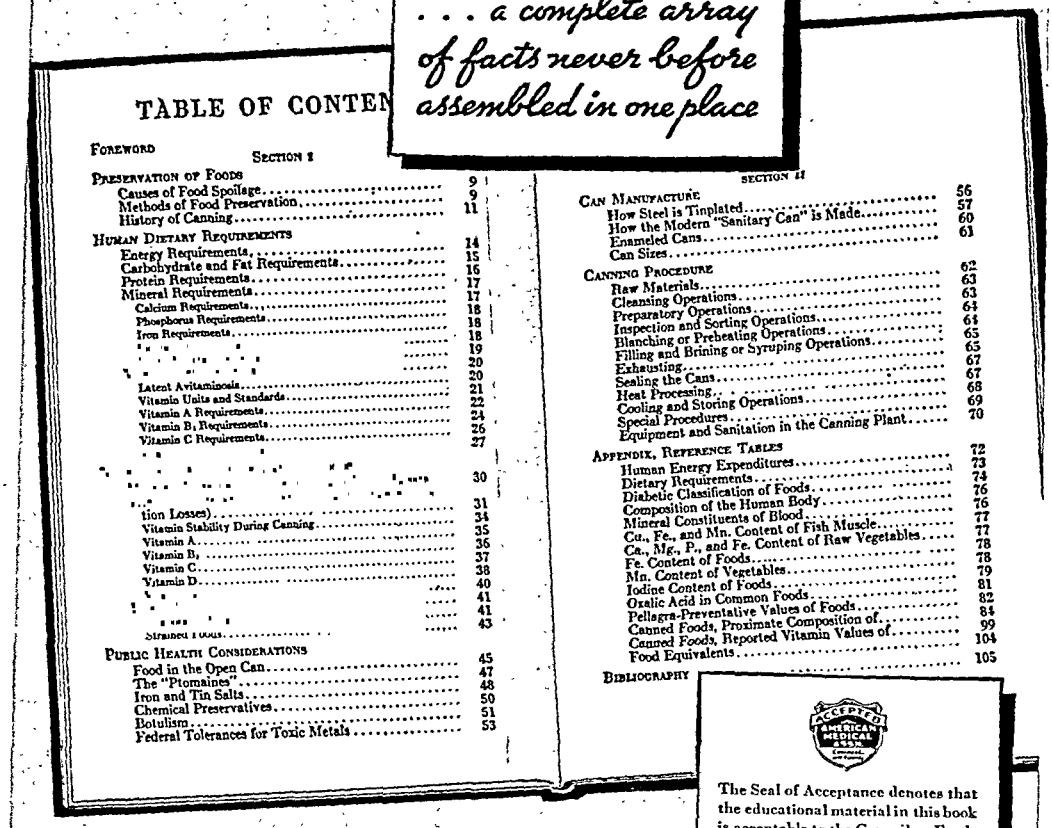
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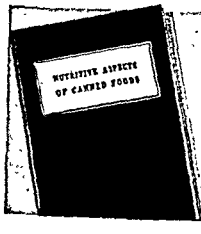
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marked by a two and one-half inch filling defect in the sigmoid was demonstrated by barium enema and X-ray. Also there was a gross polypoid involvement of the entire colon, sigmoid, and rectum. Sympathectomy and X-ray therapy were chosen instead of colectomy.

At operation December 10, 1935, there was found a kink due to attachment of a peritoneal fold across the sigmoid to the lateral abdominal wall and a small adhesion between the ileum and uterus. These were freed and the presacral nerve with its branches was resected. On January 3, 1936, the patient was treated by X-ray. The next menstrual period was normal as to flow and pain. Complete obstruction occurred February 16, 1936, due to temporary lodgment of released "polypoids" in the sigmoid. After four days she passed large polypoid masses and was relieved. X-ray examination of the colon March 12, 1936, showed it to be normal. The patient now has one or two bowel movements daily and the menstrual periods are normal.

Reviewer's Note:

Hirschsprung's disease has been treated by sympathectomy with a fair degree of success, at least temporarily. Some cases fail to respond and in those which do the permanency of the result has not been proven.

The result reported in a case of polyposis treated by X-ray is probably explainable on the basis of the histologic structure of the growths. Biopsy in such favorable cases usually reveals tissue predominantly lymphoid in structure and not the usual adenoma.

Wayne W. Flora, Chicago.

RIGDON, R. H.

Production of Colitis in the Dog with Staphylococcus Toxin. Arch. Path., 23:5, 634, May, 1937.

Rigdon and Leff previously described hemorrhagic and necrotic lesions in the intestinal mucosa of each of two children dying of staphylococcus aureus toxemia. One child had had otitis media, mastoiditis and meningitis; the other osteomyelitis of the tibia and acute pericarditis.

It is known that necrosis and hemorrhage in the mucosa of the gastro-intestinal tract may follow intravenous and oral administration of staphylococcus toxin. In the series of experiments reported, staphylococcus toxin was injected into the colons of twelve normal dogs. This toxin was prepared by growing a hemolytic strain of staphylococcus aureus in veal infusion broth. A 0.02 c.c. volume of the toxin produced hemolysis of 2 c.c. of a 1 per cent suspension of rabbits' red blood cells in physiologic solution of sodium chloride, and 0.1 c.c. injected intracutaneously into a rabbit produced an area of necrosis measuring 2 by 4 cm. In the dogs 0.1 c.c. to 0.5 c.c. of the prepared toxin were injected into the submucosa and mucosa of the colon in different places to the amount of 4 to 6 c.c. in different animals. The animals were sacrificed in from one to fourteen days. During the first six to ten hours after operation the dogs experienced cramps and loose stools, but soon recovered and ate normally. Hemorrhage into and necrosis of the mucosa and stroma followed the injections of the toxin. After desquamation of the necrotic mucosa, ulcers were left which healed in from eight to fourteen days. These lesions were similar to those previously described in the colons of rabbits and dogs following intravenous injection of staphylococcus toxin. They were also similar to those found in the gastro-intestinal tracts of the two children dying of staphylococcus toxemia. The necrosis of the skin of the rabbit following intracutaneous injection of the toxin was also similar, which would make it appear unlikely that there should be two fractions in the toxin, one a "skin-necrotizing" and the other a "gastro-intestinal" toxin.

N. W. Jones, Portland.



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On request we shall be glad to send you reprints of the four articles referred to in the article mentioned above, viz.: 1—Hanning, Flora: Canned Strained Vegetables as Sources of Vitamin A, J. Am. Dietet. A., 9:295 (Nov.) 1933. 2—A Comparison of Vitamins B and G in Canned Strained Foods, J. Nutrition, 8:449 (Oct.) 1934. 3—Further Studies of the Content of Vitamins A and B in Canned Strained Vegetables, J. Am. Dietet. A., 12:231 (Sept.) 1936. 4—Comparison of the Biological and Chemical Methods for the Determination of Vitamin C in Canned Strained Vegetables and a Study of Its Variation From Year to Year, J. Nutrition, 12:405 (Oct.) 1936. Write Gerber Products Co., Dept. 339, Fremont, Mich.

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GALL, EDWARD A.

The Response of Guinea Pig Bone Marrow to Liver Extract. Amer. Jour. Path., XIII, 4, 575, July, 1937.

The author refers to the work of Jacobson, who showed that normal adult male guinea pigs, fed a diet of oats, carrots and lettuce, react to the administration of liver extract by the development of a significant increase in the number of the circulating reticulocytes. This response, if constant and consistent, would offer a means of biological assay of the potency of liver fractions. Other investigators, however, have questioned the reliability of the test. In the present paper is given the results of a study of the marrow of the guinea pig under several experimental conditions undertaken to determine the effect of liver extract, and if possible to explain the above mentioned disagreement.

Five groups of guinea pigs were studied. Ten animals fed a diet of oats, carrots and lettuce showed densely cellular marrow with evidence of depressed maturation of its cells. Seven animals thus fed and showing marked depletion of cellular elements revealed abruptly accelerated maturation following the administration of a single dose of liver extract. Two other animals similarly fed showed persistent increased maturation on a daily dose of liver extract for 6 and 10 days respectively. Twenty guinea pigs fed on a diet of hay, oats and carrots did not show a depression or inhibition of maturation of the marrow cells, which led to the conclusion that a diet of hay, oats and carrots possessed a substance available in liver extract, but that it was absent in a diet of oats, carrots and lettuce. The nature and source of this substance, whether it is the food substance or vitamin content of the hay or from the molds growing in it, is not determined. Nor is it known whether lettuce contains some inhibitory factor. The general conclusion to be drawn from the study is that guinea pigs under controlled conditions may be found to be a satisfactory means of assaying liver fractions. Changes in the bone marrow elements responded in the main to the rise in the circulating reticulocyte count as reported by Jacobson.

N. W. Jones, Portland.

REDISH, JULIUS

Hodgkin's Disease of the Stomach with Fatal Gastric Hemorrhage. Arch. Path., 23:6, 844, June, 1937.

Lesions of the wall of the stomach due to Hodgkin's disease are rare. The first case was reported by Schlagenhaufer in 1913. Redish finds the records of twenty-two cases, which were confirmed by autopsy, in the literature, to which he adds one more. The gross appearance of the stomach in the different cases has varied; some have shown diffuse infiltration, some bulky tumor masses and ulcerations.

The case now reported was that of a 54 year old white man, who presented himself at the hospital for the removal of a painless enlarging mass of the anterior thoracic wall. He was well nourished and complained of no symptoms of illness. Four days after entering the hospital he vomited a large quantity of bright red blood and died two days later. On the lesser curvature of the stomach there was found an ulcer measuring 7 cm. in diameter. The margin was elevated and thick. The base consisted of firm, grayish-white tumor-like tissue, which shaded off gradually into normal gastric wall. A second and similar ulcer, 2 cm. in diameter, was in close proximity to the other. The peripancreatic lymph nodes, spleen and anterior wall of the chest were involved in the process. The histologic picture of tissues from these organs was characteristic of Hodgkin's disease. Many large mononucleated and multinucleated giant cells were present. Clinically the case was of interest because of the absence of symptoms and sudden death from gastric hemorrhage. Pathologically it was of particular interest because of the rarity of the lesion.

N. W. Jones, Portland.

ALT, HOWARD L. AND SWANK, RAY L.

Thrombopenic Purpura Associated with Catarrhal Jaundice: Report of a Case. Annals of Inter. Med., Vol. 10, pp. 1049-1053, Jan., 1937.

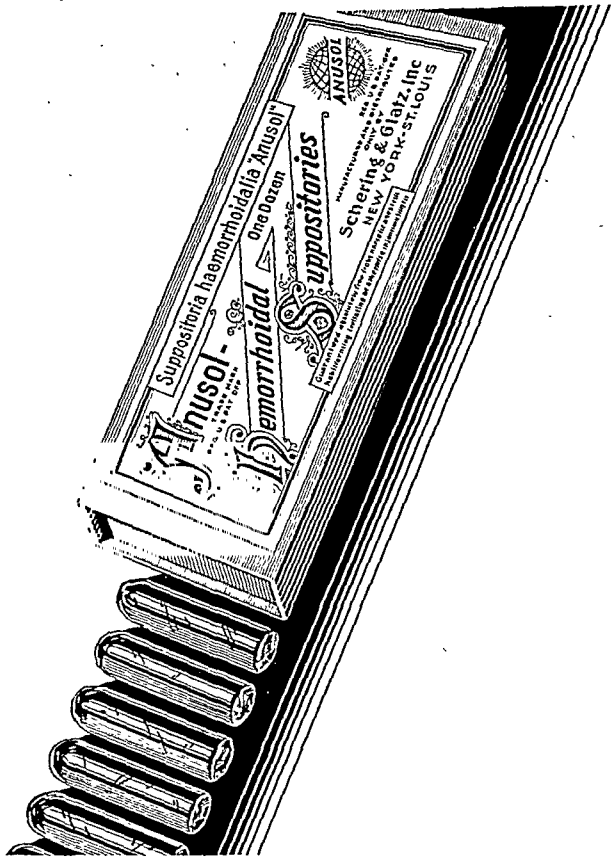
A patient has been observed in whom an acute thrombopenic purpura occurred simultaneously with an acute catarrhal jaundice.

A male, age 24, was admitted to the hospital complaining of malaise, epistaxis and jaundice which followed an upper respiratory infection one month before, and the gradual development of anorexia, muscular aching, constipation, discomfort in abdomen, highly pigmented urine, lighter colored stools and petechial spots for three days prior.

The significant laboratory data show an absence of blood platelets; no clot retraction; increased bleeding time; 3+ bile in the urine; a strongly positive benzidine test for occult blood in feces and in urine; increased quantitative *van den Bergh*; increased icterus index and a marked increased dye retention on functionally testing the liver. On duodenal intubation and administration of 100 c.c. of magnesium sulphate, a thin greenish mucoid secretion was obtained.

The patient was treated by transfusion of citrated blood and a injection of whole blood. Subsequently calcium gluconate, viosterol, and liver extract were given each day. He became entirely well and was discharged from the hospital three weeks after admission. There has been no recurrence of symptoms one and one-half years after the illness occurred.

Accompanying this report is a discussion of the etiologic relationship between thrombopenic purpura and catarrhal jaundice. Also evidence is



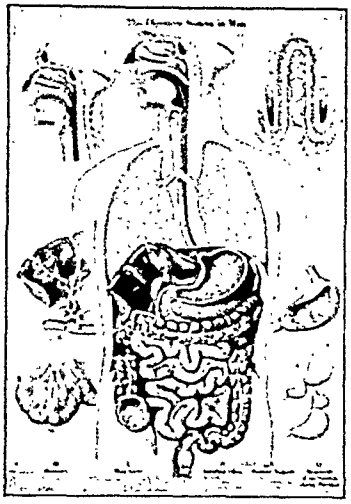
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presented which suggests a relationship between thrombopenia and liver disease.

B. B. Vincent Lyon and C. W. Wirts.

FISKE, F. A. AND AEGERTER, E. E.

Primary Carcinoma of the Liver Cells with Peritoneal Metastasis. Arch. Path., 21:1, 58, July, 1937.

Although primary carcinoma of the liver is not particularly a rare tumor, the authors review briefly the literature and report a case of primary liver cell carcinoma, as distinguished from primary carcinoma of the small biliary ducts, because of extensive peritoneal metastasis—an unusual occurrence.

In brief resume certain points of clinical interest may be gleaned from the paper. Primary cancer of the liver of both types are most frequently found in Orientals. Seventeen per cent of all cancer deaths in the Philippines fall into this group. Cirrhosis is a common accompaniment—85 per cent with carcinoma of the liver cells and 50 per cent with carcinoma of the bile ducts. The tumor is more frequently found in the right lobe, and the right diaphragm is often fixed. The liver may be smaller than normal by reason of the accompanying cirrhosis. Jaundice occurs in 61 per cent. Pain, fever, ascites, edema and enlarged spleen are frequently noted. Extrahepatic metastasis has been found in only 20 per cent of the cases. For this reason surgical removal has been successful in a fair percentage of cases and is a procedure to be recommended.

The case reported presented massive metastasis throughout the peritoneal cavity. The mode of spread seemed to be through the lymph vessels.

N. W. Jones, Portland.

HIRSCH, EDWIN L.

Primary Lymphosarcoma of the Liver with Metastases to the Marrow and Secondary Anemia. Arch. Path., 23:5, 674, May, 1937.

The author reports a case of primary periportal lymphosarcoma of the liver with extensive metastases to the bone marrow by way of infiltration through the walls of branches of the portal vein. The case seems to be the second one of primary lymphosarcoma of the liver on record. The first case was reported by Sternberg (1934) and was believed to have originated on the basis of aleukemic lymphadenosis (pseudoleukemia). The lymphoid tissue of the liver, which is sparse in amount, rarely becomes malignant.

In the reported case the tumor cells were small, round and compressed, and resembled lymphocytes. They penetrated the walls of large and small divisions of the portal vein in many places. The lumens of the vessels contained thrombi of tumor cells, which were evidently dislodged easily by the blood stream. The walls of the bile ducts were also invaded in places. The extensive invasion of the bone marrow led to much destruction of the original marrow cells, and this fact was the probable cause of a severe, intractable secondary anemia, which had been uninfluenced by any kind of therapy.

N. W. Jones, Portland.

STEWART, H. L., CANTAROW, A. AND MORGAN, D. R.

Changes in the Liver of the Cat Following Ligation of Single Hepatic Ducts. Arch. Path., 23:5, 641, May, 1937.

The authors undertook the study to determine the comparative effects of obstructing single lobes of the liver of the cat with those of total obstruction. Seventeen cats were used in the experiments. One or more ducts leading from the left lobes were obstructed and the tissues were studied after periods of stasis from one day to five months. Their conclusions were that the changes in obstructed portions of the liver following ligation of single hepatic ducts are, with few exceptions, essentially similar to those which result from ligation of the common bile duct. The changes are, however, less marked and less rapidly progressive. The cirrhosis is monolobular; focal necrosis is less and appears later; the hepatic cells at the periphery of the lobules contain little or no stainable lipid although the interior cells may contain much; lobular atrophy progresses inward from the periphery; repair and re-



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*Oelgetz, A. W., Oelgetz, P. A., and Wittekind, J.: Studies in Bowel Drainage, Am. J. Digest. Dis. & Nutrition 3:549 (Oct.) 1936.

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generation of hepatic cells occur throughout periods of stasis up to sixty-two days; mitotic figures are most numerous between the twelfth and thirty-fifth days; there is no difference in the amounts of stainable lipids in obstructed and non-obstructed lobes with periods of stasis up to sixty-two days; and occasionally impaired liver function may occur following ligation of single ducts.

N. W. Jones, Portland.

SCHLOSS, J., ETTINGER, A. AND PRATT, J. H.

Diagnosis of Diseases of the Stomach by Gastroscopic and X-ray Relief Studies. Abstracted from Am. Jour. Med. Sci., Feb., 1937.

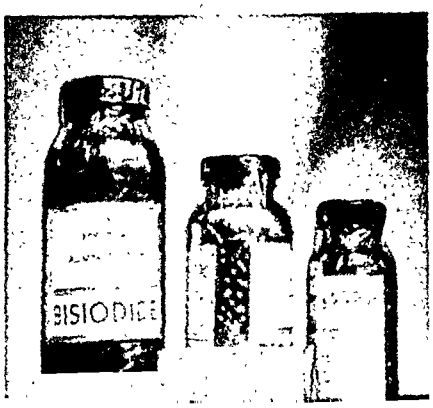
During the last two decades morphologic evidence of the condition of the stomach wall has increased considerably the number of correct diagnoses as proved by biopsy and necropsy. The authors present studies on a hundred cases examined by X-ray relief method and gastroscopy. The essentials of both procedures are discussed at some length and it is stated that we may expect the X-ray examination is superior where localized lesions, if not too small, are present; whereas generalized pathological processes and very fine superficial changes are more the domain of the gastroscope. The lesions which X-ray examination fails to reveal can usually be visualized with the gastroscope, while those which can scarcely be seen by gastroscopy seldom cause difficulties for the roentgenologist.

In discussing gastritis the writers note that in the recent American literature, gastritis does not find as prominent a place as in the European and they have felt that the more general use of both X-ray relief technique and gastroscopy in Europe is responsible for this discrepancy. X-ray diagnosis of gastritis is usually based upon indirect signs such as hypersecretion, hyperperistalsis, broadening and increased rigidity of the rugae; it rarely succeeds in demonstration of the so-called "granulated relief." These "granula" are direct signs of hypertrophy and correspond to the "wart-like" swellings of the mucosa seen by gastroscopy, which method also shows direct signs of gastritis representing epithelial changes such as spongy velvet-like appearance of the surface, edema, circumscribed hyperemia, old and fresh hemorrhages and verrucous swellings. The enlarged fold is due to functional changes of the submucosa and muscularis mucosae rather than to true gastritic processes (Forsell, Henning). The most impressive X-ray sign is a frequent but not a constant finding in hypertrophic gastritis. Schindler subdivided the anatomic picture into three groups: Superficial, hypertrophic and atrophic gastritis. Actually features of the different groups of Schindler's classification are seen in the same case of chronic gastritis. Henning expresses this in the gastroscopic diagnosis. The authors feel that two types should be discussed separately: i.e., the gastritis with multiple erosions and the complete atrophy without demonstrable signs of chronic inflammation. They saw that pain and other symptoms disappeared as the erosions healed. The patient was kept on a strict diet until the erosions were gone. The symptoms do not always correspond with the gastritic changes found; they may be mild in one case and pronounced in another instance; the constitution, psyche and personality of the patient playing an important part in his subjective reaction to the disease. The authors feel that the X-ray of atrophy is more or less guesswork and tables are given to prove this. Generalized lesions of the stomach are more easily diagnosed with the gastroscope. Regarding gastric ulcer small lesions which the writers classify as erosions, are more accurately diagnosed by gastroscopy than by X-ray. They mention that Gutzeit found in 100 cases of gastric ulcer the diagnosis was possible in 45 cases by X-ray and in 75 by gastroscopy; agreeing with the writers' experience in a small number of cases.

As to the diagnosis of carcinoma of the stomach there

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was in the authors' series satisfactory agreement between X-ray examination and gastroscopy. Post-operative stomachs usually show severe gastritis changes. Among the conclusions drawn by the writers are these: The combined use of X-ray relief technique and gastroscopy is an additional help in diagnosis and in the investigation of unsolved problems in the pathology of the stomach. For the diagnosis of gastritis, gastroscopy is by far superior to X-ray relief technique. Erosions and atrophy of the stomach mucosa can be diagnosed for all practical purposes by gastroscopy alone. For the diagnosis of stomach tumors and post-operative changes, X-ray relief method and gastroscopy supplement one another in an almost ideal way.

Allen Jones, Buffalo.

HEERMANN, S. J. AND GINS, JOHN A.

Hyperinsulinism Associated with Calcified Tumor of the Pancreas. J. A. M. A., Vol. 108, No. 17, pp. 1402-1405, April 24, 1937.

Hyperinsulinism due to excessive doses of insulin was originally described by Banting and his associates in 1923. Since that time many cases of spontaneous hyperinsulinism have been reported. It is characterized by nervousness, tremor, hunger, anxiety, sweating, fatigue, emotional instability, incoordination of the finer movements, vasomotor phenomena, such as pallor, flushing, confusion, difficulty of articulation, syncope, collapse, and unconsciousness. Convulsions may occur. Gastro-intestinal symptoms simulating ulcer, irritable colon, cholecystitis, pancreatitis, appendicitis and many cases classified as gastric neuroses.

The author reports a case of a man who complained of weakness, chilliness, headache, vertigo, blurring of vision, and collapse. Dyspnoea on exertion developed later. He lost thirty-five pounds of weight over a period of three years. Emotional instability was noticed by his family. Physical examination was essentially negative. A glucose tolerance test was done and a diagnosis of hypoglycemia was made. An exploratory operation for a pancreatic tumor was done, and a hard, calcareous tumor was found in the head of the pancreas and removed. The patient recovered from the operation and the glucose tolerance test became normal with the disappearance of the previous symptoms.

Francis D. Murphy, Milwaukee.

HOLMAN, CRANSTON.

The Diagnosis of Gastric Carcinoma and Peptic Ulcer. J. A. M. A., Vol. 108, pp. 1383-1385, April 24, 1937.

The diagnosis of gastric cancer has been made easier by the improvement in X-ray technic, but nevertheless it still is a difficult problem. Because of this, the examination of the gastric contents has been carefully carried out on 152 cases. The method used is that suggested by Bloomfield and Polland. It is made after fasting twelve hours with histamine used as a stimulus in a dose of 0.1 mg. to each 10 kg. of body weight.

The fasting contents are withdrawn, the histamine is injected subcutaneously, and the stomach contents are continuously aspirated for thirty minutes, and the contents divided into three ten-minute specimens. The greatest ten-minute volume of secretion and the highest titratable acidity attained are considered the indexes of gastric function.

The conclusions drawn from the results in these 152 cases are that a low or anacidity is strong evidence of carcinoma; a normal or high acidity points to ulcer. This method of diagnosis was found to be more accurate than other methods.

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Artificial Fever in the Treatment of Ulcerative Colitis: A Preliminary Report*

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THE frequent discouraging results obtained in the treatment of ulcerative colitis are well known to all those who have had patients suffering from this disease under their care. In a considerable experience in the treatment of this disease we have been unable to confirm the work of those authors who look upon ulcerative colitis as the result of an infection by a specific organism. In our therapeutic efforts, we have noted, as have others, that those procedures which were associated with the production of a fever gave the most beneficial results. Thus, in the use of vaccines or sera, a therapeutic effect was noted in proportion to the reaction which followed the injection of these foreign proteins. Likewise, blood transfusions which were followed by a post-transfusional reaction appeared to give more immediate results than those which were uncomplicated by a chill or a rise in temperature.

Because of these observations, we decided to try treating ulcerative colitis by artificial fever produced by the Kettering hypertherm.† The treatment was begun as an experimental procedure, and during the period of therapy no other treatment for the colitis was given except a smooth diet.

The air-conditioned cabinet known as the Kettering hypertherm uses the principle of radiant heat to elevate the patient's temperature, humidified hot air being circulated around the body. This apparatus has been described in the literature frequently (1), so that repetition here seems unnecessary. In treating patients with ulcerative colitis, we were using the non-specific effect of fever, i.e. its general effect on the body's defense mechanisms, rather than its specific killing effect on an organism, as in gonococcal infections. We felt, therefore, that relatively short fever sessions at relatively low temperatures would be as effective as long sessions at high temperature levels. Our usual method of treatment consisted of 2½ to 3 hours of fever between 104° F. and 105° F. (rectal), 3 times a week. The number of treatments varied between 7 and 17, the average being 12 per patient.

The early and continued improvement noted in all of the patients we have treated made a preliminary report of this method of therapy seem worth while in spite of the fact that we do not as yet have a large series of cases.

SUMMARY OF CASES TREATED

1. A. S., black female, 19 years. History of bloody diarrhea in fall of 1934 and spring of 1935. Admitted 11/12/35, complaining of loose watery bowel movements, as many as 20 daily, often containing blood.

11/15/35: proctoscopic examination showed the mucosa of the lower 20 centimeters of large bowel to be red and thick, dotted with small ulcers which bled on slight trauma. Culture of the ulcers showed Strep. viridans and B. coli. Feces were negative for parasites or ova. It was suggested that fever therapy be given.

11/29/35: first fever treatment.

12/3/35: patient much improved after 3 fever treatments, having about 8 movements per day. Proctoscopic examination showed mucous membrane to be still edematous, with bleeding on slight trauma.

12/18/35: condition much improved after 9 treatments; 4 to 8 partially formed movements daily. No blood.

12/20/35: proctoscopic examination showed marked improvement in the bowel. Ulcers now practically healed, except in a few areas. These show definite evidences of healing.

12/29/35: patient discharged from hospital; 3 to 4 movements daily.

Follow-up 4/13/36: 4 movements daily. No bleeding. Proctoscopic examination showed bowel normal in appearance, except for slight contraction of the lumen.

1/22/37: patient perfectly well and at work as a maid until present time, a year after treatment. Began to have 2 to 4 movements a day, occasionally with slight bleeding. Examination showed a granular mucosa, somewhat narrowed bowel lumen, no ulceration. Patient feels perfectly well. Was advised to have further fever therapy but refused because of economic conditions.

2. F. H., white male, 31 years. Admitted 7/22/36 with a history of bloody diarrhea 8 years before admission and complete relief until April, 1936, when he began to have frequent stools following the flood in Pennsylvania. Bowel movements 15 or more daily, liquid and containing blood; often containing clots and associated with left-sided abdominal pain and tenesmus.

7/24/36: proctoscopic examination showed lumen of bowel narrowed and mucosa thickened and dotted with small ulcers which bled easily on slight trauma. Culture: B. coli and Strep. fecalis.

7/22/36 to 9/4/36: patient had various types of medical treatment, during which time he had little or no improvement, with bowel movements ranging from 5 to 23 daily, average about 8 to 10.

9/5/36: first fever treatment.

9/14/36: patient's diarrhea had stopped and he was having 3 to 4 movements daily with no bleeding from the bowel.

9/18/36: after 6 treatments the mucous membrane still showed marked inflammatory reaction and bled easily on slight trauma. Mucopurulent exudate.

9/28/36: after 10 fever treatments, patient was having 2 formed bowel movements daily. Clinically almost well.

10/23/36: after 17 fever treatments, proctoscopic ex-

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†These cabinets are being used at the Philadelphia General Hospital through the kindness and cooperation of Dr. Walter M. Simpson, Director of the Kettering Institute for Medical Research, Miami Valley Hospital, Dayton, Ohio

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amination showed somewhat granular mucosa. All the ulcers were healed. No blood or pus seen.

10/24/35: patient discharged, symptom-free. One to 2 bowel movements daily.

No follow-up.

3. M. A., white female, 24 years. Admitted 11/11/35, complaining of diarrhea; 5 to 10 movements daily. The stools seemed to be almost pure blood and bowel movements were associated with abdominal pain. In addition, marked weakness and dizziness, loss of 15 pounds of weight. Proctoscopic examination showed diffuse hyperemia with granular mucosa but no ulcerations. Bowel bled easily on slight trauma. Lumen of the bowel reduced. Culture showed B. coli, Strep. viridans, Strep. fecalis.

11/30/35: after 3 fever treatments, patient having two partially formed movements daily with no bleeding.

12/6/35: after 5 treatments, one formed movement daily. No symptoms. Proctoscopic examination showed the edema and hyperemia of the lower bowel and rectum to have practically disappeared. Patient was given 4 more fever treatments.

5/8/36: patient returned, three months pregnant. Bowel was normal in appearance, but she had slight bleeding from a few small internal hemorrhoids.

10/12/36: patient delivered. No bowel symptoms during pregnancy, except slight constipation relieved by mineral oil.

Follow-up 3/3/37: no further complaints.

4. P. N., white male, 36 years. Admitted 10/17/36, complaining of sudden appearance of diarrhea, one week's duration, with 20 to 30 liquid stools daily. Loss of 25-30 pounds in weight.

10/23/36: proctoscopic examination showed purulent exudate covering the mucosa of the rectum and lower bowel. Marked hyperemia of mucous membrane, with irregular superficial ulcerations which bled easily on slight trauma.

10/29/36: first fever treatment.

11/4/36 to 11/11/36: no fever treatments because of respiratory infection.

11/11/36: after 6 fever treatments, 8 to 9 formed movements daily. No mucus or blood.

11/27/36: proctoscopic examination still showed some edema and hyperemia of bowel. Ulcers healed. Seven fever treatments given. Patient refused further therapy.

12/11/36: 3 to 4 movments daily. Gained 20 pounds in past two weeks.

12/17/36, symptom-free. 3 to 4 movements. Proctoscopic examination showed slight contraction of bowel, otherwise bowel appeared normal. Patient has been observed frequently; last time 3/5/37. Local examination shows no lesions. Patient is having no symptoms.

5. A. A., white female, 27 years. Admitted 6/25/36 with history of colitis for 6 years, with remission during two pregnancies. The colitis appeared in attacks lasting two to three months at a time. Bowel movements numbered 8 to 10 daily, with blood and mucus. Proctoscopic examinations showed a diffuse acute inflammatory reaction of the rectum and lower colon, with marked edema and hyperemia and bleeding on the slightest trauma. Cultures were taken which showed the Bargen organism. Patient was treated with transfusions and intensive calcium gluconate therapy by mouth and generalized ultra-violet irradiation. Vaccines of Bargen's organisms were given from August to October, 1936. During this time patient improved somewhat; then she developed a cold. Bowel movements increased in number to 8 to 10 daily. Proctoscopic examination showed a diffuse hyperemia of the mucous membrane of the rectum; bowel contracted; haustral folds obliterated. Mucous membrane granular in appearance and bled easily on slight trauma. There were no frank ulcerations.

1/29/37: first fever therapy.

2/12/37: after six treatments, patient was having 1 to 3 movements daily with no bleeding. Proctoscopic examination still showed a diffuse granular appearance of the mucous membrane with bleeding on slight trauma. The lumen was much contracted.

2/23/37: after 11 fever treatments, 1 to 2 movements daily. No symptoms. Proctoscopic examination showed very marked improvement of bowel. The intensely red granular appearance of the bowel noted at last examination was changed to a more normal pink color. Still some residual narrowing of the lumen.

3/8/37: patient discharged symptom-free. Bowel practically normal in appearance.

Comment: All of these cases appeared to give the typical clinical and proctoscopic findings of idiopathic ulcerative colitis, and each one has responded very favorably to fever therapy. The clinical improvement has preceded the improvement in the proctoscopic appearance. In most cases, after 3 to 4 fever treatments in 7-10 days, the number of stools was markedly reduced and bleeding and tenesmus were less. The patients' appetites improved and their weights began to increase. In spite of the clinical improvement, we have continued the fever treatments until the proctoscopic appearance has also improved, except in one patient, case number 4, who refused to have more than 7 fever treatments. In this patient, the appearance of the bowel on proctoscopic examination continued to improve, in spite of the fact that his fever treatments were not continued. This has raised the question in our minds as to whether the fever treatments may be discontinued as soon as clinical improvement is well established, with the expectation that the bowel will continue to improve until it reaches or approaches the normal. In later cases it is our intention to stop the fever treatment when clinical improvement is well established.

The use of artificial fever in the treatment of ulcerative colitis is not regarded as a treatment which will produce a permanent cure, but it has been the method which has produced the most rapid clinical improvement in our hands. This short preliminary report is made in the hope that others may try this type of therapy.

We wish to express our appreciation to Dr. R. S. Boles, Dr. F. J. Kalteyer, Dr. S. A. Loewenberg, and Dr. David Rieman for their permission to include these patients in this report. We also wish to express our appreciation to the nurse-technicians, Miss Eileen McCarthy, Miss Isabelle Michler and Miss Edna Mae McTague, who gave the fever treatments under our direction.

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Studies in Intermittent Heat Sweats
The Chlorides and the Acid-Base Balance

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THE loss of hydrochloric acid through vomiting has long been recognized as a means of producing alkalosis. McCollum (1) and his co-workers, in 1920, were able to produce gastric tetany and alkalosis in dogs by mechanical obstruction of the pylorus. They were able to prolong the lives of these animals by administering sodium chloride. Later, Maizels (2) and Tucker (3) demonstrated similar states of alkalosis in patients suffering from functional or organic obstruction of the stomach resulting in excessive loss of chlorides from vomiting.

Simpson et al. (4) in their work on the ultra high frequency pyretotherapy of neurosyphilis, found that the patients lost from two to five liters of sweat during the five hour febrile period. The plasma chlorides were found to have declined an average of 40 mg. per cent in 80 per cent of the patients at the end of the febrile period. In five instances the fall exceeded 100 mg. The average sodium chloride content of the sweat was 650 mg. per cent, 20 to 26 grams of sodium chloride being lost during the five hour period. The hydrochloric acid disappeared from the stomach within thirty to ninety minutes.

One of the patients developed typical hypochloremic tetany while others experienced nausea, vomiting, fatigue, abdominal cramps and muscular twitching. These symptoms were largely abolished by the ingestion of four to six liters of .6 per cent sodium chloride solution.

Beck and Dill (5) in 1932, and Schofield (6) in 1933, during the work on Boulder Dam, found that physical activity at high temperatures produced great loss of chlorides and water. Bischoff et al. (7, 8, 9) concluded from their experiments that an alkalosis was produced by diathermy, short radio waves, or external heat. The pH of the plasma was elevated above the normal reading for the quinhydrone electrode and the alkaline reserve increased. Hopkins (10) also observed a rise in the plasma pH with temperatures of 105° over a thirty to forty-five minute period, but an average decrease in the carbon dioxide combining power.

These states of alkalosis may be explained in part by the loss of carbon dioxide through hyperventilation and of lactic acid in the sweat, the regulatory mechanisms of the body apparently being unable to compensate for such rapid losses. Hopkins (10) accounts for the diminished carbon dioxide combining power in her subjects by a shift of the bicarbonate ions from the blood into the tissues and urine, and an increased stability of acid oxyhemoglobin as the carbon dioxide tension of the plasma fell.

The following experiments were designed to study the effect of a series of short sweat periods upon the chlorides and the acid-base balance, allowing a rest period between each sweat for the body to adjust itself to the losses encountered. Such repeated sweats compare in a measure with the intermittent sweating engaged in normally during hot summer days, and to the periodic sweating present in certain fibrile diseases.

EXPERIMENTAL PROCEDURE

The experiments were conducted during the cold months of the year when normal sweating is at a minimum. Fourteen normal adult subjects, 18 to 37 years of age, were given four 20 minute sweat periods in a hot dry room in which the temperature varied from 140° F. to 160° F. One-half to one hour of rest was allowed between each period. The skin of each subject was prepared before each sweat period by thorough cleansing with soap and water, alcohol, and ether, and the sweat collected from the chest and back by gently scraping the skin from below upward with the open mouth of a large test tube. The subjects were carefully cautioned to limit the sweat sample to the eccrine type and to avoid as far as possible contamination with the apocrine type of sweat. About 75 c.c. of sweat was collected for analysis from each subject during each of the four periods. These sweat samples nearly filled the vessels, which were tightly stoppered and the sweat analyzed within a short time (two to three hours). The temperature, pulse rate, blood pressure and weight of each subject were recorded before and after each period. Samples of venous blood for the determination of the CO_2 combining power and chloride content were taken before and after the completion of the tests.

Fluids were given in all but two subjects, in the form of a mixture of orange juice, lemon juice, and water, the chloride content of which was 8 mg. 100 c.c. Beer was substituted for the fruit juice in two instances containing 3.1 mg. of chloride per 100 c.c. The total amount of fluid allowed each subject was 1000-1500 c.c. and no fluid was given after the second sweat period.

All urine passed during the entire period of observation was collected, a specimen being obtained for analysis at the end of each period. No stools were passed and the respiratory losses were not determined. The approximate sweat loss was calculated from the

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equation: *sweat loss* equals *weight loss* minus *urine loss* plus *fluid intake*.

RESULTS

1. The majority of the group complained of a headache, a feeling of oppression, and exhaustion, but only one member was overcome, lost consciousness for a minute and discontinued the tests. This occurred during the fourth period. A few subjects were nauseated, one member vomiting a pint of fluid after the experiments were over. He suffered from a severe throbbing headache throughout the tests.

2. The blood pressure readings fell into four groups. In five subjects the systolic pressure tended to rise throughout the four periods, the average elevation being 10 mm. of Hg. In two subjects the same level was maintained, while in five subjects it tended to fall: the total drop averaging 11 mm. of Hg. In the two remaining instances it rose during the first two periods and fell during the last two.

The variations in diastolic pressures corresponded in general to the systolic except in subjects G and D; in whom the initial readings were low and beer had been substituted for the fruit juice mixture. In these subjects the diastolic pressure was indeterminate during the first two periods, but returned to normal levels in the fourth period.

3. The pulse rates increased in all subjects, the average rise being 24 beats per minute. The temperature readings (oral) were elevated from .2° to 3.2° F., with an average increase of 1.5° F. The maximal changes in temperature occurred in the earlier periods.

4. The chloride concentration of the sweat (Table I) increased in the later periods in all subjects except one, the average chloride loss for the four periods being 7222 mg. The urine chlorides, (Table I) however, became progressively less with each period, although the concentration in the specimens after the fourth period was usually increased over the preceding one. The average urine chloride loss was 1,062 mg. The total chloride loss from each subject averaged 8284 mg., the chloride intake ranging from 31 mg. to 120 mg., the average net chloride loss being 8184 mg. The blood chlorides (Table II) were decreased an average of 12 mg. per cent. In nine subjects they were decreased, remained constant in three, and were elevated in two.

5. The CO_2 combining power of the blood (Table II) increased in seven subjects, remained constant in one, and was depressed in five, the average for the group being a rise of 1.4 Vol. per cent.

6. The pH of the sweat varied from 4.8 to 8.6, the average of the initial specimens being 6.42 and the final specimens 6.67. In twelve of the fourteen subjects the pH tended to increase with successive sweatings, while in only two instances was the final pH less than the first.

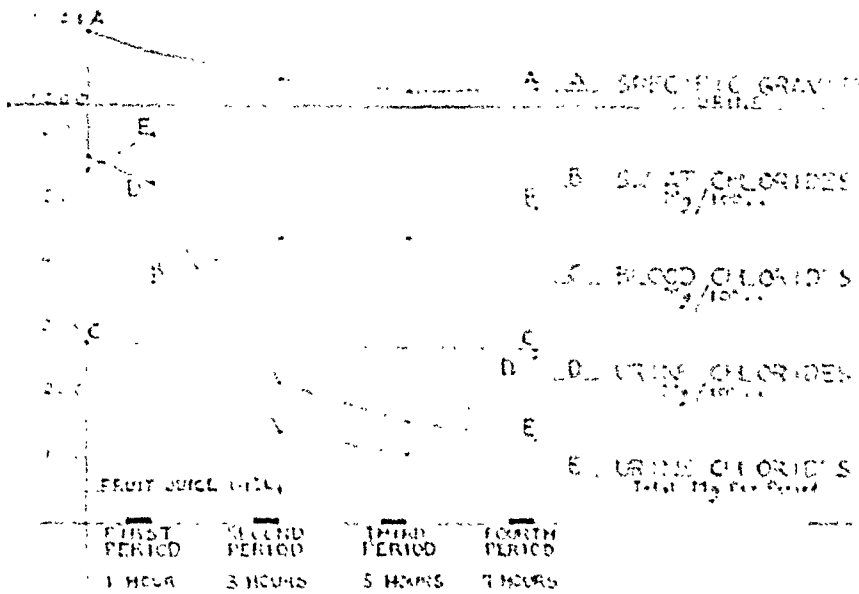
The pH of the urine varied from 4.4 to 6.7, the group average being elevated in the second and third periods and dropping below the original level in the final period. The average of the initial specimens was 5.47 and the final group 5.2.

7. No sugar or albumin appeared in the urine tests. The specific gravity fell during the second and third periods from an initial 1.020-1.030 to 1.001-1.006. In two subjects the fourth period reading was 1.020, but the remainder of the group maintained the low levels.

8. The net fluid loss ranged from 680 c.c. to 1,400 c.c.

Chart 1

The effect of sweat periods on the chlorides



DISCUSSION

Under the conditions of our experiments large quantities of chlorides were excreted in the sweat, the concentration of the sweat chlorides in general increasing with each period, while both the chloride concentration and total chloride content in the urine

tended to decrease with each period (Chart 1). This low chloride content of the urine was associated with a low specific gravity. It is difficult to explain the rising chloride concentration in the sweat and corresponding fall in the urine, inasmuch as the average blood chloride concentration was decreased only 12 mg./100 c.c. and in two instances was increased (Chart 1).

Simpson (11) observed a 40 mg. per cent decrease in the plasma chlorides in 80 per cent of a group following a five hour continuous febrile period, which suggests that the rest periods in our series made possible a mobilization of the chlorides from the tissues. The ingestion of 1,000 to 1,500 c.c. of a fruit juice not an infallible indication as to the presence of alkalosis but only indicates the alkali reserve of the blood. The variability of the plasma alkaline reserve must depend in part on mobilization of alkali from the tissues, which varies with the individual's tissue reserve. It is significant that Hopkins' fever periods were much shorter than those of Bischoff.

In twelve of the fourteen subjects the pH of the sweat tended to increase with each successive period, suggesting a compensatory mechanism to combat the tendency toward alkalosis present in heat sweat experiments.

The symptoms of headache, vertigo, nausea, vomiting and exhaustion which arose during our experi-

TABLE I

	Urine Chloride Before tests	Loss in mgm. During tests I	II	III	IV	Total Urine Exer. cc	Total Ur.Cl Exer. mgm	Sweat Chloride Loss in mg/100 cc I	II	III	IV	Total Weight Loss	Total Fluid Intake cc	Total Sweat Loss cc	Total Sweat Cl. Exer. mgm	Total Chlorides Exer. Fluid(mgm)
A	mg/100 cc 344	640	171	30				307	328	466	392					
	Total 858	192	102	12		130	306					.68 K	1500	2050	7646	7952
B	mg/100 cc 525	527	93	124	217			361	485	401	425					
	Total 787	422	187	136	195	480	940					.99 K	1300	1810	7566	8506
C	mg/100 cc 493	*	340	417	417			459	475	279	505					
	Total #	#	#	#	#							.46 K	1500			
D	mg/100 cc 716	661	53	36	177			397	459	471	464					
	Total 215	1322	106	54	88	600	1570					.68 K	1500	1580	7078	8648
E	mg/100 cc 716	709	59	137				374	533	440	540					
	Total 286	567	324	479		980	1370					.46 K	1500	980	4625	5995
F	mg/100 cc 808	518	80	35	241			354	429	445	448					
	Total 606	1632	200	52		715	1884					.46 K	1500	1245	5216	7100
G	mg/100 cc 659	683	83	106	278			534	573	629	541					
	Total 395	307	145	48	139	315	639					.46 K	1375	1520	8649	9288
H	mg/100 cc 667	650	28	44	51			136	785	693	604					
	Total 667	650	99	49	77	710	875					1.40 K	1300	1990	11024	11899
I	mg/100 cc 548	518	132	277	*			429	358	507	528					
	Total #	#	#	#	#							.99 K	1500			
J	mg/100 cc 431	344	56	20				333	237	299	735					
	Total 431	206	44	20		240	270					.99 K	1300	2050	8220	8490
K	mg/100 cc 401	155	35	0				374	297	322	435					
	Total 501	46	53	0		310	99					.50 K	1300	1670	5962	6061
L	mg/100 cc 475	447	364	75	82			487	551	526	535					
	Total 356	313	182	244	164	645	903					.99 K	1500	1845	9686	10589
M	mg/100 cc 502	273	179	170	565			129	133	136	140					
	Total 1380	846	1029	612	141	1270	2628					.99 K	1500	1220	1635	4263
N	mg/100 cc 695	752	268	98	326			558	562	541	534					
	Total 695	752	186	246	81	445	1266					1.15 K	1000	1705	9360	10626
Ave.	mg/100 cc 570	529	139	112	261			374	443	439	487					
	Total 548	604	221	162	127	570	1062							1639	7202	8284

* Samples of urine lost.
** Drank beer instead of fruit juice.
Samples of urine not measured.

SWEAT LOSS equals WEIGHT LOSS minus URINE LOSS plus INTAKE

mixture, or beer, replaced but a small portion of the chloride loss resulting in an average net loss of 8184 mg. Results indicate that such fluids wash the tissue salts out in the sweat, the depletion rising rapidly with any increase in sweat loss, the kidneys tending to conserve the diminishing chlorides of the body.

The carbon dioxide combining power of the blood became elevated in but seven of the thirteen subjects, the average for the entire group constituting a rise of 1.4 volumes per cent. Bischoff et al, (7, 8, 9) concluded in their hyperpyrexia experiments that the alkali reserve was increased, while Hopkins (10) reported an average decrease in the carbon dioxide combining power. Since both reported plasma pHs above normal limits, it would appear that the CO_2 C.P. is

ments in some of the subjects, closely parallel those observed by Hench, Slocum and Popp (12) in their prolonged hyperpyrexia experiments, and by Hardt and Rivers (13) in their cases of alkalosis following the excessive administration of alkalies. In our group, however, the temperature and blood pressure range was small, and evidence of only mild alkalosis was present. These symptoms in our series may have resulted from the marked depletion of chlorides from the tissues. Simpson et al (4), in the pyretotherapy of neurosyphilis, found these symptoms abolished by the administration of .6 per cent sodium chloride.

In diseases with intermittent febrile periods and sweats such as tuberculosis and malaria, and in the normal intermittent sweating on hot summer days,

TABLE II

	Total Chloride Intake	Total Chloride Loss	Net Chloride Loss	Blood Chlorides			Plasma CO2 C. P. Vol %		
				Before Tests	After Tests		Before Tests	After Tests	
A	120	7912	7832	280	280	0	58.9	59.8	+ .9
B	104	8107	8403	300	296	-04	55.7	61.7	+ 2.1
C	120			293	317	+19	61.7	63.2	+ 1.5
D	120	8648	8528	291	280	-11			
E	120	8998	8878	286	271	-15	61.2	59.1	- 2.1
F	120	7160	7040	286	271	-15	56.8	61.7	+ 4.9
G*	45	7287	7242	286	286	0	56.7	58.7	+ 2.0
H	104	11897	11793	289	272	-17	64.7	71.6	+6.9
I	120			276	259	-17	61.2	71.0	+ 9.8
J	104	8190	8086	274	257	+17	62.2	69.6	+ 7.4
K	104	6871	6767	327	170	-57	54.7	54.2	- .5
L	120	10169	10049	286	278	- 8	57.6	57.0	- 2.6
M	120	4262	4142	286	240	- 4	55.4	67.3	+12.9
AVG.	91	8284	8164	291	272	-17	59.5	63.7	+ 3.6
AVG.	107.5	8284	8164	291	272	-17	59.5	63.7	3.6

* Drank beer instead of fruit juice.

an opportunity is present for the blood to replenish itself at the expense of the tissues, and blood chemistry studies will not reveal the extent of the depletion of tissue chlorides. Such depletion may play an important role in lowering the resistance of the individual.

CONCLUSIONS

1. Excessive sweating results in a marked loss of chlorides from the tissues.

2. During repeated heat sweats the chloride concentration of the sweat increases while that of the urine decreases.

3. The pH of heat sweat tends to increase with succeeding periods of sweating.

4. In intermittent heat sweats the tissue chloride depletion is much greater than the blood chloride content would indicate.

The authors wish to express their appreciation to Dr. A. J. Carlson of the Department of Physiology, University of Chicago, for his help and suggestions in this work.

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Food Habits of the Patient with Peptic Ulcer

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FROM time to time articles appear in the literature which suggest that peptic ulcer may originate from faulty diets. Various writers have suggested that inadequate amounts of vitamins may be responsible for this disease (1) of which, vitamins A and B have been particularly stressed. There is also a sufficient amount of other evidence to make one consider some form of deficiency as a cause of this disease. Aron, Weiss and Holtzmann (2) reported that injections of histidine would prevent the development of ulcer in dogs, upon which they had performed an operation similar to that introduced by Mann and Williamson, although recently, Sandweiss (3) has been unable to confirm this work. The successful production of experimental ulcers in dogs has followed operations which have sidetracked or depleted the animal of its important digestive juices, such as the pancreatic, biliary, and duodenal secretions (4). The obvious explanation for the development of ulcers following these procedures has been an inadequate neutralization of the gastric juices; yet, it nevertheless follows that such procedures must disturb the animal's digestion and may produce some kind of deficiency. In a recent paper, Ivy (5) has reported a series of animals fed on a diet which included raw pancreas who did not develop ulcer following a Mann-Williamson operation.

The justification of considering that ulcer may result from a deficiency appears warranted, if one compares its behavior with pernicious anemia which is now known to be caused by a deficiency. Both are chronic diseases characterized by remissions and exacerbations. It is accepted that pernicious anemia occurs in certain constitutional types, and Draper and others (6) have stressed the importance of constitution in the etiology of peptic ulcer. Therefore, it seemed worth while to study a group of patients with peptic ulcer with the purpose of determining whether they showed an inadequate dietary, either in a general way, or for specific foods.

METHOD OF STUDY

Food histories have been taken on 25 patients suffering from either a gastric or duodenal ulcer and on 25 controls. A chart was made out in which the various types of foods were grouped under the heading of meat, fish, eggs, milk, butter, fruit, vegetables, cereals, bread, relishes and deserts. Places were left for checking any food eaten and whether it was taken once a day, once a week, once a month, or less often. The last place enabled the patient to write in how much of each food was taken at one serving. In the beginning these outlines were given to the patients to fill in, but it was found impossible to get satisfactory reports from even the most intelligent patients, if they were allowed to fill in the questionnaire themselves. Therefore, each patient was questioned by one of us (M. E.), who then filled in the answers as the questioning proceeded. By this means we were able to obtain what we believe was sufficiently accurate data on the individual's diet. Similar studies were made on 25 other individuals serving as a control, about half of which were taken from patients on the surgical wards and in whom there was no reason to suspect dietary disturbances. The remainder was made up from friends living outside the hospital.

After the data had been accumulated, it was decided to express all the food factors in terms of the amount taken per day. This is the method usually employed in referring to protein, carbohydrate and fat, and it seemed best to express all the other dietetic factors in the same way. In order to obtain an idea of the relative intake of vitamins, these have been reduced to a unit value. The method which we used for doing this has the advantage of being easy and was satisfactory because we were interested only in determining the relative amount of these substances which were taken by the different groups. The vitamin content of a given food is expressed in most food

TABLE I

Showing the dietetic factors present in two "Normal" diets, and the amounts of these factors actually ingested by 25 patients with peptic ulcer and 25 controls

Factors	Normal No. 1	Normal No. 2	Ulcer Patients	Controls
Protein	105.5	78.	90.9	74.7
Fat	157.5	144.0	118.4	87.9
Carbohydrate	334.5	225.	246.8	239.4
Calories	2997.	2320.	2421.2	2049.6
Calcium	1.518	1.268	.897	.765
Phosphorus	1.932	1.405	1.418	1.221
Iron	.0165	.0153	.018	.012
Vitamin A*	154.8	118.	106.04	101.79
Vitamin B	144.0	96.	99.23	90.77
Vitamin C	95.4	64.	67.36	67.07
Vitamin G	146.8	103.	95.21	89.64
Acid	32.9	28.0	34.10	31.39
Base	37.4	31.1	46.71	35.64

*See text for calculation of vitamins.

tables by plus marks, varying from one to four. If an arbitrarily chosen weight of food is considered to contain that number of plus signs given in a food table, a relative unit of intake may be reached. We used 25 grams as an arbitrary measure of the food. If a patient ate 25 grams of butter, he was considered to have ingested 3 plus

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vitamin A and one plus vitamin D. If he ate 100 grams of butter he would have ingested four times the amount, or 12 plus vitamin A and 4 plus vitamin D. By this method it is possible to calculate the relative intake of vitamins for one day and thus obtain a comparative figure for all patients.

Because the taking of a food history may involve a personal equation so far as the attitude of the history-taker is concerned, it seemed best to have some check on the accuracy of our histories. As a control we calculated the amount of food ingested on theoretically normal diets. For this purpose two diets were studied. One was made up by one of us (M. E.), the other was taken from a leaflet made up by a group of dietitians under the direction of Miss Frances Sterne. The results from both so-called normal diets were calculated before the results from our food histories were obtained. As will be seen from a study of the tables, the diet of Miss Sterne provided an appreciably greater intake of food than the one made up by us. Perhaps the difference can be explained by the fact that Miss Sterne's diet is supposed to represent an ideal diet; whereas, ours is an expression of what we believe the average normal patients eat.

TABLE II

Shows how 25 patients with ulcer and 25 controls distributed their intake. The figures express the number of servings per week which these individuals averaged

Foods	Ulcer Patients	Controls
Meat	7.32	8.21
Fish	2.2	1.44
Fats	4.4	4.48
Milk	2.53	2.67
Butter	24.2	22.28
Eggs	3.24	3.32
Oysters	2.68	4.04
Vegetables	10.46	12.04
Refined Cereal	9.32	7.37
Coarse Cereal	2.4	3.56
Dark Bread	13.13	13.52
White Bread	2.8	3.15
Relish	2.3	2.3
Dessert	2.3	2.2

RESULTS AND DISCUSSION

Table I shows the relative amount of various food factors which would be taken if a patient had eaten the two theoretical diets, and the amount eaten by our group of normal patients and those with an ulcer. If one compares the diet taken by the normal and the patients with ulcer, it is apparent that there is not much difference between them. On the whole the ulcer patients consumed a greater amount of all the substances than the normals, which is most easily shown by the fact that the ulcer patients on the average, ingested 2421.28 calories, whereas, the normals took 2019.68 calories. The ulcer patients averaged 99 grams of protein daily, which is certainly an adequate amount. The ulcer patients also tended to take an adequate intake of fat, which averaged 118 grams per day in this series. The intake of minerals as represented by calcium, phosphates and iron was also somewhat higher among those with ulcer than among the normals. Vitamin C was the only factor which was consumed in smaller amounts by the ulcer patients than the normals, namely, 67 units per day, as opposed to 87 units. However, there is no reason to feel that this represented an inadequate amount of this vitamin. A comparison of the dietaries determined by our food with the theoretical diets shows no evidence for a deficient intake. Although there were slight differences in the amount of vitamins taken, these were not such as to appear significant.

Table II shows the relative amounts of different types of food taken by the normal persons and those with an ulcer. Again, the differences seem to be of a minor order and do not have any apparent significance. A study of the individual items of food taken by the two groups showed that the patients with ulcer had as varied a choice of foods as the normal individuals.

SUMMARY

From this study, therefore, there seems to be no evidence that patients with an ulcer take an abnormal diet as concerns the total amount of the various food factors with which we are now familiar, nor do they take an unbalanced diet in the sense of eating certain articles of food to the exclusion of others.

It seems reasonable to deduce, therefore, that if peptic ulcer is the result of some form of deficiency, that deficiency occurs not from faulty food habits but from the lack of some intrinsic factor.

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The Treatment of Peptic Ulcer by the Diet of Goldberger and Wheeler*

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SINCE the studies of Pavlov, clinicians have attempted to influence the gastric acidity of patients with peptic ulcer by dietetic measures, but diets high in fat and low in proteins or carbohydrates do not decrease the acidity sufficiently to be of practical value. It is known now that food may also affect the acidity by its content of vitamins. If it should prove to be possible to control the acidity by regulating the intake of vitamins without producing undesirable effects, a useful addition to the therapeusis of peptic ulcer would be attained.

The best approach to this problem seemed to be by means of the diet which Goldberger and Wheeler used to produce pellagra. It is now generally accepted that pellagra is the result of a deficiency, and in 1915 Goldberger and Wheeler were able to produce experimental pellagra by giving volunteers a diet which contained only those foods on which patients had been observed to develop the disease. The diet was low in animal protein, and consisted chiefly of white wheat flour, cornmeal, hominy grits, cornstarch, white rice, granulated cane sugar, cane syrup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens, and coffee. With this diet, 6 of the 11 volunteers developed pellagra within 194 days. The average protein content varied between 41 and 54 grams; the fat between 91 and 134 grams; and the carbohydrate between 387 and 513 grams.

Since their original work, Goldberger and Wheeler and their associates have tested a number of other foods for the pellagra preventive factor by experiments on dogs. From these studies they have discovered that several of the foods used in their original diet were relatively good sources of the pellagra preventive factor, and using this work as a basis, they have since made up a diet which is more efficient in the production of this disease.

It seemed to us, for several reasons, that this diet might be useful for treating patients with ulcer. Goldberger found that by a judicious use of the diet he was able to keep his dogs at any stage of the disease that he wished. Thus, he could maintain them in a condition bordering on pellagra without, at the same time, actually producing the disease. It is known that quite a number of patients with pellagra have an achlorhydria. Although the relationship of the disease and the achlorhydria is not yet clear, it is possible that a diet which will produce pellagra may also lower or abolish the gastric acidity. If the gastric acidity could also be controlled in the same way that these investigators controlled the pellagra, the physician would command a useful procedure. Therefore, we determined to try a group of volunteers suffering with peptic ulcer on the diet of Goldberger.

Since we started this investigation, Alvarez, Pilcher, Foley, Mayer, and Osterberg have reported the results of a study with a similar object in view. They attempted to control the production of hydrochloric acid by a diet low in vitamin B_1. They obtained no definite change either in the gastric acidity or the pepsin concentration and concluded that a diet deficient in vitamin B_1 by itself was not likely to produce much reduction in gastric acidity. Because the diet of Goldberger is not deficient in vitamin B_1 and is different from that of Alvarez and his associates, we continued our work.

METHOD OF STUDY

This study was carried out in the Gastro-Intestinal Clinic of the Out-Door Department of the Peter Bent Brigham Hospital. We chose only those patients who were intelligent enough to understand the object of our investigation, and only after we had explained fully the nature of our study, and that it was purely experimental.

Five patients volunteered to take the diet. Each patient was given a typewritten copy which had been made up by the dietitian, and on which the various foods were grouped according to the amount of pellagra preventive factor, as determined by Goldberger. They were allowed prunes, oatmeal with sugar and salt, baking powder biscuits, butter, black coffee, fat salt pork, Irish or sweet potatoes, floured gravy, beets, navy beans, American cheese, coffee, jello, carrots, boiled rice, evaporated apples, cornmeal mush, and cornmeal muffins made out of white cornmeal. The patients reported once a week, at which time their weight was taken and the hemoglobin and red blood cell count was determined. Gastric analyses were made every two or three weeks, and a test meal of 60 c.c. of 8 per cent ethyl alcohol was used, the specimens being titrated in the usual way with Topher's reagent and phenophthalein.

Goldberger found it difficult to get prisoners to follow the diet even with the promise of a pardon in return for their cooperation. In spite of this fact, we were able to obtain data which seems to us worthy of consideration.

PRESENTATION OF DATA

Because of the variation in the way the patients followed the diet, the divergence of results, and the small number of cases which were studied, it seems that the data can be presented best by a summary of each case.

Patient R. H. ODD. 184,170 was a 30-year old white male with a history of periodic attacks of symptoms of ulcer for four years. Roentgenologic examination showed an irregular duodenal cap with bilateral notching, and a demonstrable crater. There was definite tenderness over the ulcer. He was placed on a Sippy diet with relief from symptoms. After two weeks of the Sippy diet he was

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given the experimental diet with alkaline powders every two hours during the day. He was maintained on this diet for 63 days. The first six weeks he lost three pounds, but he did not complain of weakness, and continued with his work on an ice truck. He had no symptoms of epigastric distress during the experimental period. There was no significant change in the blood. The first gastric analysis done one week after going on the diet showed a fasting free acidity of 114, and a total acidity of 127. After the alcohol test meal, the free acidity was 55 with a total acidity of 68. After nine weeks on the diet there was no decrease in acidity. Then the patient refused to continue the diet because of his distaste for the food. Except for one or two occasions when the patient admitted eating meat, he followed the diet satisfactorily, so far as we know. He was free of symptoms during the whole experimental period.

Patient P. B. ODD. 182,110 was a 42-year old white male with a history of ulcer symptoms of 12 to 15 years' duration. Eleven years previously he had an operation for a perforated duodenal ulcer, and since that time he had suffered from frequent attacks of ulcer distress. Roentgenologic examination revealed a constant deformity in the duodenal cap, a bilateral notching, and a definite crater. For several months previous to this study, the patient had been taking frequent doses of milk and powders without relief of his symptoms. He was started on the experimental diet and was followed for 125 days. During the first twelve weeks he lost four pounds but varied very little thereafter. A red count at the beginning of the study was 4,200,000. Nine weeks later it was 5,200,000. He used 6 to 8 alkaline powders a day throughout the experimental period. The first gastric analysis showed a fasting free acidity of 16 and a total acidity of 32. Following the test meal the free acidity was from 11-52 and the total acidity 50-64. During the first two weeks of the diet he continued to have considerable epigastric distress both during the day and night. During the third week, however, he began to feel much better, and continued to be comfortable until he had a recurrence of the ulcer distress twelve weeks later. The gastric analysis done after three weeks and nine weeks showed no significant variation from the original test. After ten weeks on the diet the roentgenologic examination showed the irregularity of the duodenal cap, but no crater could be visualized. The diet was then increased to allow one serving daily of string beans, lettuce or turnips, food graded as "slight" in the pellagra preventive value. After twelve weeks on the diet the gastric analysis showed no significant reduction. In spite of this fact the patient was more comfortable than at any time in the previous six months. Foods somewhat higher in their pellagra preventive value were gradually added. He returned two weeks later complaining of nocturnal distress. Because he was not desirous of going back to the original diet, he was given skimmed milk to be taken at hourly intervals during the day with alkaline powders at intervals of a half hour. One week later he felt better, but a week after this complained of much epigastric distress. He was then given a Sippy diet in place of the experimental one. At no time did this patient develop symptoms or physical signs of pellagra. We believe that he followed the regime faithfully. He was symptom-free for some period of time after following the diet. We cannot give any reason for this relief.

Patient N. B. ODD. 185,117 was a 38-year old white male with a history of epigastric distress for four and a half months previous to the time we saw the patient. Six weeks before our seeing him his duodenal ulcer perforated and was closed. At the time he came under our observation he was having no distress, and a roentgenologic examination showed a small, contracted, irregular duodenal cap with no demonstrable crater. Gastric analysis showed no free acidity in the fasting specimen and a total acidity of only 7. After taking a test meal the free acidity was 51 and the total acidity 58. He was maintained on the experimental diet for 56 days. During that time he lost no weight and did not complain of epigastric distress. The gastric analysis after five weeks on the diet showed essentially the same findings as before. As he had no distress before starting the diet and none while taking it, it was impossible to make him follow a strict regime.

In contrast to these three patients who followed the diet with moderate comfort, there were two others who were unable to continue because of a recurrence of epigastric distress.

Patient J. V. ODD. 181,643 was a 46-year old Italian laborer who had had intermittent abdominal distress for three years. Roentgenologic examination showed thickened gastric rugae and an irregular duodenal cap. Gastric analyses showed a persistently high acidity, the amount of free acid always above 65 and the total acid above 70. Previously he had been following a Sippy diet with relief. He was placed on the experimental diet but suffered a return of pain and went back to the Sippy diet after two days.

Patient C. E. ODD. 172,619 was a 32-year old Italian housewife who had been followed in the Gastro-Intestinal Clinic for two years. Roentgenologic examination showed an irregular asymmetric duodenal cap and a definite crater. In March, 1926, she had a return of her symptoms and was placed on a Sippy diet. One month later she was quite comfortable, although she still had the nocturnal distress. She was placed on the experimental diet, and one week later complained of a return of severe epigastric distress. Skimmed milk was added to the diet at hourly intervals. Although this gave some relief, she was unwilling to continue the experimental diet and was allowed to go back on the Sippy regime. Both of these patients were nervous Italians and objected particularly to the diet, quite aside from the question of discomfort.

DISCUSSION

A review of the data reveals that no positive results were obtained by putting the patients on the experimental diet. In no case was there a lowering of the gastric acidity, a change in the blood, or a development of any evidence of pellagra. Perhaps the patients did not follow the diet closely enough or for a long enough time. Whatever the reason, it seems evident that it is impractical to treat patients with peptic ulcer by this diet. We believe that some of the patients followed it as closely as any person would do, unless some great inducement such as a cure could be offered. One patient was maintained on the diet as long as 125 days without any positive results. It is possible that a longer period of observation might have produced changes, but we did not wish to carry them to the point of developing pellagra. Goldberger and

Wheeler kept their eleven volunteers on a similar diet for 194 days. Six of these developed definite signs of pellagra, but did not do so until after 160 days of the diet. We considered that 125 days was a sufficiently long period to test out the practical application of the diet and still not run the chance of producing pellagra. We were interested in the relative degree of comfort which some of the patients enjoyed while on the diet. However, no conclusions can be drawn from this fact because it is well known that patients suffering from a chronic disease may develop temporary relief after starting a new regime.

CONCLUSION

Five patients with a duodenal ulcer were placed on a diet low in the pellagra preventive substance, with the object of trying to reduce the gastric acidity. Two of these followed the diet for a period of several days. Two followed it for an average of 59 days, and one as long as 125 days. None of the patients developed any change in their gastric analysis or blood findings. Two of the patients had temporary relief which we could not associate with the diet. Although it seems possible that such a diet might be used to reduce the gastric acidity, if a study could be carried out under more carefully controlled conditions, it appears impractical to use such a diet for the treatment of patients with peptic ulcer.

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Dental Caries and Paradental Disturbances*

III. The Dietary History and Its Value in Dental and Medical Practice*

By

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IN the course of studies being carried out in the College of Dentistry at the University of California on the relation of diet to dental problems an endeavor has been made to secure as accurate a dietary history as is possible from the patient, or from the patient's mother in case of a child. Since few of us recall many details regarding our food habits before the age of 15 years or so, whenever possible, even in the case of adults, we have interviewed the patient's mother (personally or by correspondence) regarding these early years.

We were fully aware, before we attempted to take dietary histories of patients, that the experience of most persons, who have endeavored to learn what a person's food habits have been by questioning the individual, has been rather disappointing. But we were very anxious to secure such data so have attempted to work out a technique which gives a by and large estimate of an individual's nutritional background. As a result of this experience it is believed that in most instances it is possible to secure a fairly accurate (in a relative sense, of course) estimate of the present and past nutritional record of an individual, provided sufficient time, and a moderate amount of tact and diplomacy are used.

However, it is not intended to give the impression that the degree of accuracy of interpretation of results, such as one expects in animal research, is possible. But the data have shown that it is possible to say in most instances whether or not unsatisfactory nutrition may be a factor in the etiology of the disorder, which has brought the patient to our attention. Furthermore, it is possible to evaluate the various dietary factors (in a general way) which in turn gives a rather clear picture as to which dietary essentials have been present in smallest amounts. Paper IV of this series will discuss the problem of the evaluation of the dietary history.

The fundamentals of an adequate diet and the foods supplying them have been known for several years. But a detailed dietary study of approximately 450 persons suffering from various dental and medical disorders has shown that very few of these persons are taking a satisfactory diet. In most instances studied the reason was not a financial one. The reason appeared to be a lack of an understanding that one of the prerequisites for optimum health is that the diet should contain liberal amounts of all dietary factors. It is fully recognized that a diet may contain adequate (liberal) amounts of all dietary essentials but, due to the body's failure to assimilate them, malnutrition or even deficiency diseases may result. It cannot be stressed too often that the mere fact that an individual is not suffering from one of the deficiency diseases is no indication that his (or her) diet is optimum from a nutrition standpoint. Although we fully appreciate that (1) poor mouth hygiene, (2) endocrine disturbances, (3) hereditary factors, (4) developmental defects, (5) general health and (6) lack of professional care, often complicate dental problems, we question whether the newer knowledge of nutrition is as yet being applied by the majority of persons; we do not believe that optimum nutrition on a large scale over a period of years (except among

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certain primitive peoples) has been given a chance to show what it can do in the prevention of dental disorders. However, it appears that there are certain dental problems which are primarily inheritance problems over which nutrition has little or no control. An example in point: certain enamel problems. That all persons are not capable of the same degree of health (which in turn also refers to dental health) is undoubtedly true; in other words, inheritance may and in many instances does set a limit to what a person is capable of from a health standpoint. Economics may or may not complicate one's health problem.

In the light of the experience in taking about 450 dietary histories, a series of questions has been formulated which forms part of this paper. No one is more cognizant than the author of the fact that the usual answers to questionnaires are frequently not of great value, but it is not intended that this set of questions be given to a patient. They are for the guidance of the dentist, the dietitian, the physician, or other persons sufficiently trained to take dietary histories. Naturally all questions do not apply to all patients. As soon as one is familiar with the many factors which may enter into the nutritional background of an individual, the questionnaire can be dispensed with, but until one is familiar with the technique it serves as a reminder of important points.

The questionnaire is divided into several parts: Part I consists of eleven questions which apply to the diet and health of the mother and also to the general health of the family. Part II (to be answered by the mother, if possible) is concerned directly with the food habits of the individual up to about 15 years of age. This section is further divided into two parts: (1) dietary habits up to the age of 6 years; (2) from age 6 to 15 years of age. Ages are relative of course. Part III is devoted to "Some Health and Hygiene Factors" which may or may not complicate the nutrition problem (to be answered by the mother, if possible). Part IV consists of questions to be answered by the patient, i.e., food habits in general after 15 years of age. Part V is composed of questions relative to "Health and Hygiene Factors" which may have complicated the nutrition problem from about the age of 15 to the present time. In all instances the age division is relative. It has been found that the majority of persons interviewed recalled in a general way their food habits after the age of 12 to 15. They did not remember details of menus of course, but any individual even before the age of 12 knows whether the family lived on a ranch (and the kind of a ranch, fruits, stock, wheat, or dairy, etc.) a small farm, in a village where it was possible to have their own cow, a few chickens, and possibly a few fruit trees, or whether the family lived in a city where all foods had to be purchased. This information is of importance in a nutrition history due to its bearing upon the food supply of the family.

Unless the income is rather large such foods as milk, meat, butter, eggs, fresh and canned vegetables are not used so abundantly, due to the cost, as they are when available on a farm. In other words, in many instances all that is necessary is to secure the "nutritional set-up" of a family, and with a moderate amount of experience one can estimate with a fair degree of accuracy, as human studies go, what the food supply has consisted of. Personal likes and dislikes must always be taken into consideration; an abundance of food of high nutritive value may have been available but due to a personal idiosyncrasy (not necessarily an allergy) the individual has not taken the type of diet he or she could so easily have taken.

If the market orders of a family appear to contain an abundance of high nutritive value foods, this does not necessarily mean that an individual has taken a highly satisfactory diet. But if the market orders over a considerable period of time are known to have been inadequate (and there has been no outside source of food) naturally the diet of the individual members must have been inadequate. The statement that all persons sat at the same table and so must have eaten the same diet has long been known not to be true; amount of food eaten and likes and dislikes complicate the problem.

Not infrequently a person has had two or more periods in his life from a dietary standpoint. For example, an individual may have been born on a ranch and lived there for the first 15 years of his life. Milk, eggs, butter, fruits and vegetables were abundant; he liked these foods and ate liberal amounts of them. He was out of doors a great deal especially in summer so sunshine played its part as a source of vitamin D. No severe illnesses complicated his childhood. From the age of 15 to 40 he may have lived in a city with an entirely different set of conditions as regards his food supply and outdoor life. These details are very important from the standpoint of a dietary history.

Another person may have had an entirely different childhood even though he did live on a farm. He may have had a long series of illnesses which not only complicated his nutrition problem but also kept him from leading the active outdoor life of a country child. Another patient may be one of a family of six or more children who lived in a city on a small income. Dut to expense, milk, butter, cheese, eggs, meats, fresh or canned fruits, and vegetables had to be used in small quantities; cereals and their products being less expensive foods, had to be used in greater abundance. The mother may not have known enough about food values to spend the food money as wisely as it could have been spent. Cereals and their products are primarily energy foods. If a patient recalls that from an early age he has taken either or both tea and coffee, one is fairly safe in estimating that less milk has been consumed than is believed necessary for a child, due in part to the limited quantity of the fluid intake. In other words, each patient must be considered as an individual. It often takes considerable time and patience to learn the many factors which have played a rôle in an individual's nutrition-set-up.

DIETARY HISTORY

Patient No. ..... Date.....
Name..... Telephone No.....
Address..... Nationality.....
Date of birth..... Language spoken.....
Place of birth..... Height..... Weight.....
Type of body build: Slender.....Normal.....Stocky....

Width-Weight: (Consult Width-Weight Tables for Boys and Girls; Men and Women; of Helen B. Pryor, M.D., Stanford University Press, Stanford University, California).

PART I

The following 11 questions apply to the MOTHER of the patient, or to the general health of the family.

1. What was the state of your health during the 10 years before the patient was born?.....
If not in good health, please name illness or illnesses and treatment .....

2. What were your dietary habits a few years *before your pregnancy* for the patient, *during the pregnancy* and *while nursing* in respect to:

a. Meats, including fish (name kinds).. . . .
b. Eggs .....
c. Vegetables (fresh and canned) ....
d. Fruits (fresh and canned) ....
e. Milk .....
f. Cheese .....
g. Cereals (which are/were your favorites) . . .
How often used? ....
h. Bread—white, whole wheat, or rye ..
i. Tea of coffee—or both .....
How many cups on an average per day?

3. Were you an out-doors person?... . .

4. Were you in good health during pregnancy for patient? .....

5. Amount of nausea: Few months?.
During entire pregnancy? ... .
If quite miserable, please make a general statement as to the amount of food retained? . . ..

6. In general what is the state of health of the various members of the family? ....
Have any of the various members of the family ever had tuberculosis? .. . .
Arthritis? . . . .
If various members of the family have had "many illnesses" please name them . . ..

7. Is there a history of deafness in the family?
If so, which members? . . ..

8. Have any members of the family had kidney stones? .. . . Bladder stones. . . . If so, which members, and at what ages? .. ..

9. Is there a history of allergy in the family—eczema, hay fever, asthma? If so, what form and which members? ... .

10. Are you (mother) of a nervous temperament?..

11. What is the dental condition of the various members of the family? ....
Grandparents: Maternal... ... Paternal . .
Father (also his brothers and sisters) . . . . ..
Mother (also her brothers and sisters) . .
Brothers (if any, of the patient) ... .
Sisters (if any, of the patient) ... .
Does the patient have better teeth or poorer teeth than other members of the family? ....
Or are his (or her) teeth above average? ....

DIETARY HISTORY

PART II
DIETARY HISTORY OF PATIENT UP TO ABOUT 6 YEARS OF AGE

The following questions in Parts II and III to be answered, if possible, by the patient's mother, father, or near relative. (Note: "you" and "your" refer to *patient* unless otherwise stated).

1. What number child are you in the family? (1st, 2nd, 3rd) .....
How much did you weigh at birth? .....
How long a time between you and previous child? .....
How many children are/were there in the family? ....

2. Were you breast fed? .....
If so, for how long? .....

3. If not breast fed, what type of formula were you given? .....
Was a preparation such as Mellin's used? .....
Horlick's malted milk?..... Cereal, gruel, plus milk ....
Were you fed a condensed milk? .....
If so, at what age and for how long? .....
Were you fed an evaporated milk? ....

4. Were you a difficult feeding problem as a baby? ..... Were you several months old (about how many months) before a diet was found to agree with you?.....

5. Whether or not you were breast-fed, about *what age* were such foods as the following given:
Orange juice . . ... How much?..... At the age of a year about how much were you being given?.....
Cod liver oil or preparations having same or similar dietary properties..... How much?... ... At the age of a year about how much were you being given?... ...
Apple sauce . . .. Prunes... ... .
Eggs ..... Meat ....
Scraped apple or other fruit such as bananas.....
Mashed potatoes..... Puréed veg. (name kinds).....

6. What other foods such as cereals, bread and butter were given and in what amounts? .... Were these foods used generously or moderately?.....

7. Did you have a good appetite as a small child under 6?. . . . Or were you one of those children who "never had any appetite?"

8. What were your candy habits before the age of 6? . . ..

9. Were you given much sugar on your cereals or in other foods, such as cocoa, up to the age of 6?.... ....
Cookies? .. .. Cake? .....

10. In general, UP TO THE AGE OF 6 YEARS, were the following foods used: Liberally? Average? or Sparingly? (If *Liberally* please mark *XXX, Average XX, Sparingly X*).
Milk—as milk, or as cocoa or other milk drinks.... .....
Milk—in custards, puddings, or in ice cream... ... .
Milk—in creamed soups, creamed vegetables, creamed meats .. ..
Eggs—as eggs .. In custards.....
Fruits—apples or oranges (please state which or if both were used) .....
. . ..
During the winter (including late fall and early spring).
During the summer (including late spring and early fall).
Cheese, if used, the kinds . ...
Cod liver oil or other preparations supplying extra vitamins A and D . Name preparations used..... .
Fish—kinds (how often used)? . ...
Cereals (name kinds used most frequently) . ....
Vegetables (name kinds) . . ..
Bread—White, Whole wheat, or Rye . .. .
Meats—kinds (how prepared) . .....
Sweet foods, such as jams, jellies, candy, honey, cakes, cookies . ...
. . ..

(Please give as much information about the use of milk, eggs, fruits, cereals, meats, cod liver oil, and sweets as it is possible to recall. Outdoor and sunshine habits will be asked for later) . . ..

DIETARY HISTORY

Between the Ages of 6 and About 15 Years

What changes were made in the diet between the ages of 6 and 15 years in regards to the foods listed below? If certain foods were used *liberally* for a few years, then *average* or *sparingly* for several years please indicate this.

Please indicate: *Liberally XXX; Average XX; Sparingly X.*

Milk—as milk or as cocoa or other milk drinks ..
Milk—as custards, puddings or ice cream.....
Milk—in creamed soups, creamed vegetables, or creamed meats .. .. Butter. . . . Eggs.....
Cod liver oil or other preparations supplying vitamins A and D ....
Fruits or fruit juices:
Oranges. . ... Apples.....
Bananas . . . . Peaches.....
Other fruits . . ..

have such as: dancing lessons, singing lessons, Scout Activities, Camp Fire Activities? .....

28. How much time do you devote to school activities, such as athletics, class offices, or dramatics, etc.....

29. In addition to your outside activities, do you go to the movies or to parties frequently enough to interfere with getting sufficient rest? .....

When do you go to the movies? .....

Do you feel tired much of the time? .....

Please give as much information as possible about the general health, the question of rest, the problem of overfatigue, or any nervous disorders which may have occurred.

DIETARY HISTORY
PART IV

The following questions to be answered by the patient when over 15 or so years of age.

Between the ages of 15 and 25 and from 25 to the present time. What has been the trend in your dietary habits in regards to the following foods?

If used almost daily please mark XXX, once or twice a week XX, and only occasionally X. (Of course, the amounts used are of importance, but as one becomes familiar with the technique of taking dietary histories, these can be estimated fairly well according to the "nutritional-set-up" of the individual. No dietary history of this nature could be more than a by-and-large estimate of a person's food habits, but it has its value nevertheless).

	Between ages 15 and 25	25 years to present time
FRUITS		
Apples		
Bananas		
Oranges		
Grapefruit		
Peaches (fresh, canned, dried)		
Apricots (fresh, canned, dried)		
Lemons		
Pineapple		
Prunes (fresh or dried)		
Also seasonal fruits, as strawberries		
CEREALS		
Favorite cereals (please list)		
Bread, white or whole grain (Average No. slices per day)		
Was rice a favorite cereal?		
Cornmeal (yellow or white)		
VEGETABLES	Between ages 15 and 25	25 years to present time
Tomatoes (fresh or canned)		
Carrots (raw or cooked)		
Lettuce and other greens		
Potatoes: White		
Sweet		
Cabbages (cooked)		
(as cole slaw)		
Onions (raw or cooked)		
String beans		
Greens: Beet, dandelion, turnip tops, spinach		
Please name ones used)		
Navy beans, or other dried beans and peas—please name which ones		
Lima beans		
Nuts, including peanuts		
MEATS, SEA-FOODS and DAIRY PRODUCTS		
Meats (including liver, etc.)		
Fish (kinds)		
Shell-fish		
Eggs, (as eggs)		
(in other foods, i.e. custards)		
Cheese (cottage)		
(other cheese)		
Milk, as milk, cocoa, and other milk drinks		
Buttermilk		
Did sour milk in any of its various forms ever enter into your diet?		
Ice cream, milk shakes, or the other fountain drinks containing milk or ice cream		
Were meats and vegetables often served creamed		
Were creamed soups or macaroni and cheese served frequently		
Were custards, or the other puddings using milk used freely for desserts		
SWEETS		
Sugar on cereals—in coffee, cocoa, etc.		
Candy		
Are you especially fond of candy of the Life Saver Type?		
Cakes and cookies		
Pies, doughnuts		

Have you taken any cod liver oil or other preparations of vitamins A and D in recent years? .....

If so, when and for how long? .....

What preparations did you take? .....

Have you taken any yeast tablets, Bemax, or the other vitamin B preparations? .....

If so, details .....

On an average how many glasses of water do you drink per day? .....

Other fluids, such as tea, coffee, fruit, or tomato juice.....

Have you any marked dislikes among foods? .....

If so, what foods? .....

As you recall your winter diet over the past 10 to 15 years (depending upon the age of the patient) was it largely one of cooked foods, for example: cereals, griddle cakes, eggs, meats, potatoes, and other cooked vegetables, bread, butter, cookies, cakes, pies, coffee, or tea or both?

In other words, was a minimum of milk, raw foods(or canned tomatoes) used? .....

Have you ever made any marked change in your diet? .....

If so, what change? .....

When? ..... Why? .....

Do you chew gum? ..... How often? .....

Do you tend to be regular in your eating habits? .....

If not, why? .....
By and large, what is your liquor consumption? .....

Please state whether AT THE PRESENT TIME you eat sparingly (S), moderately (M), or freely (F), of the following foodstuffs:

Meat	Fish	Bread White Whole Grain	Fruits (name those used most freely)	Cheese	Eggs (No. per week)

Butter	Fresh Milk	Buttermilk (glasses daily)	Cocoa or chocolate Cups daily	Potatoes	Tomatoes Raw	Tomatoes Cooked	Tomatoes Juice

Vegetables Cooked	Vegetables Salads	Cereals freely Name those used	Tea Cups daily	Coffee Cups daily	Cakes	Pies

Rich pastry	Candy	Rice	Macaroni or spaghetti	Olive oil or other salad oils	Nuts

Cigars No. daily	Cigarettes No. daily	Do you smoke a pipe? No. daily	Any other items of interest

Will the menus requested below give a fairly accurate estimate of your PRESENT food habits? .....
If not, why not? .....

Please mention the time of meals, and also the time of taking extra food. Include all candy, milk shakes, ice cream cones, nuts, fruit, etc., taken between meals.

Please submit menus for TWO WEEKS, giving the APPROXIMATE AMOUNT of food eaten at each meal, such as 1 glass of milk (8 oz. or otherwise), 1 cup of coffee with or without cream and sugar, 2 eggs, 2 medium sized servings of potatoes, average serving of meat, etc.

PART V

SOME HEALTH and HYGIENE PROBLEMS which may have complicated the NUTRITION PROBLEM. (From age of about 15 to the PRESENT TIME).

1. About what age did you stop growing? .....
Did you grow several inches between about 15 and 20 years of age? .....
How many inches? .....

2. Have you always been about your present build? ..... Or did you have a tendency toward obesity when younger? .....

3. Between what years did most of your teeth decay take place? .....

4. During the past two to three years have you had more tooth decay than for several years prior to this time? .....

5. What kind of tooth brush do you use? Hard ..... Medium ..... Soft .....
How long have you used this kind? .....

6. Do you use tooth paste? .....
If so, what kind or kinds? .....
If powder, what kind or kinds? .....

7. What changes, if any, have you made in your tooth brushes, powder, or paste during the past two years? .....

8. Have you been troubled with bleeding of the gums? ..... If so, how? ..... Has a physician ever prescribed a special diet for you? If so, for what illness? ..... Did you follow directions carefully? ..... Results? .....

9. Does your dentist say your mouth shows good evidence of mouth hygiene? .....

10. What illnesses (and of what duration were they) have you had since you were about 15 years of age? .....

11. Have illnesses complicated your nutrition problem?

12. Have you been subject to colds during the past 10 years? .....

13. Have you been chronically tired for years? .....
If so, to what do you attribute this? .....

14. During the past 10 to 25 years (depending upon age of the patient) have you been out of doors much except possible weekends? ..... If so, please give a few details as to approximate time spent in sunshine, Were you in hiking clothes, swimming suit, or in shorts? .....

15. Is your occupation now such that you spend most of your time in-doors? .....

16. Does your skin burn easily? .....
Or, do you take a tan? .....

17. How much rest do you take (sleep)? .....
Is this more or less than you have taken over the past 10 to 15 years? .....

18. Do you have time to rest an hour in the afternoon? ..... Would you be willing to do this? .....

19. Are you or have you been for several years under great emotional strain? .....
Are you inclined to worry? .....

20. If patient is a mother, how many children and what are their ages? .....
How many were breast fed? .....
For how long? .....

21. In general, what has been your state of health for the past 10 to 15 years? .....

Please mention any other items of interest pertaining to health or dietary matters not included in the above questions.

The interpretation of the nutritional history will be undertaken in the next paper. The evaluation of the various nutritive factors such as calcium, phosphorus, protein, and the vitamins will be discussed. It should

be emphasized however, that the evaluation is of course only a by and large estimate; it is obvious that it could not be otherwise. The *importance* of the evaluation of the various dietary essentials in the dietary history is likely to be *over estimated.* It is not at all necessary to attempt an evaluation but at times it is easier for a patient to understand why it is necessary to add certain foods to his diet if, for example, the point is made that his diet could be rated only Low to Fair in calcium whereas the goal should be excellent for all factors. *For practical work* the problem which is of importance is whether or not unsatisfactory nutrition may be playing a rôle in the etiology of the disorder from which the patient is suffering. When one has an understanding of the fundamentals of nutrition it is believed that if the questions listed are answered intelligently, it will be possible to say whether faulty nutrition may be a factor in the disorder.

The question of the *assimilation* of the various dietary factors is of course the all important one. The dietary history gives no information on this point except in so far as the general health of the individual may be concerned. That factors beyond the control of the individual may influence assimilation is well known. On the one hand, one may take what appears to be an inadequate supply of calcium or other dietary factor but may have extraordinarily efficient assimilation. Are these persons the exception or are they the rule? Probably the exception. On the other hand a person whose food habits are apparently excellent may be unable to utilize so effectively the elements present.

The object of asking for two weeks menus is not with the idea in mind that these menus will be an indication of the individual's food habits over the past several years. They may be, but not necessarily so. The purpose in asking for them is to learn what the person's nutrition set-up is at the present time in order to be able to make suggestions which will require the fewest changes in his routine food habits. At times of course it is necessary to make a number of rather radical changes, but experience has shown that the fewer the changes the greater the possibility of a patient adhering to the new diet. For example, if the data suggests that a person's diet is low in vitamin B and whole grain cereals and whole grain breads (so-called) are distasteful to him, it is much better to suggest another source of vitamin B such as yeast tablets even though they may be more expensive than to urge the cereal preparations. Each person's food problems are different but when it is once known what his dislikes are and what foods are difficult for him to secure for one reason or another, it is a relatively simple matter to adjust all these differences so that his diet will be optimum in all dietary factors.

In nutrition work it is not of great importance what a person ate today or yesterday but it is of importance what an individual's nutrition interests or nutrition-set-up has been for the past 10 to 20 years. Deficiency diseases are the spectacular phase of nutrition work. Many persons are unquestionably taking diets below the optimum in dietary essentials but not low enough to bring about deficiency diseases. However, borderline cases of scurvy, beriberi, and pellagra are being recognized with increasing frequency.

It is not intended to give the impression that the relation of diet to disease belongs in the field of dentistry; only a well trained physician or a dietitian working under his direction should prescribe diets for special illnesses such as diabetes, gastric or duodenal ulcer, or other conditions where diet is of special importance. But it would seem that it is entirely within the province of the dentist to suggest a more adequate diet for a patient unless, as just stated, the individual is on a special diet under his physician. One of the best books on normal nutrition is by Dr. L. Jean Bogert entitled "Nutrition and Physical Fitness." Any one interested in nutrition would profit greatly by reading it.

That factors other than diet enter into many dental and medical problems, no one would deny but by the same token that many of the distressing conditions seen by dentists and physicians have been aggravated by faulty nutrition is undoubtedly equally true.

SUMMARY

Although factors other than nutrition unquestionably play a rôle in dental and medical disorders, data suggest that knowledge of a person's nutrition-set-up is of importance in dental and medical work.

A series of questions which have been found useful in securing a nutritional history is given. When a person is familiar with the dietary properties of foods it is not a difficult matter to decide whether an unsatisfactory diet may be playing a rôle in the disorder. For practical work this is all that is necessary.

However, in a forthcoming paper the evaluation of the dietary history as regards the calcium, phosphorus, protein, and vitamin content will be discussed. The interpretation of such data is of course relative; it is obvious that it could not be otherwise.

That a person may be taking a highly satisfactory diet and yet be poorly nourished due to poor assimilation of the dietary essentials is recognized; this important point should never be lost sight of.

Syphilis of the Stomach

By

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THE diagnosis of gastric syphilis should be of interest to gastro-enterologist, internist, syphilologist, surgeon, roentgenologist and pathologist. According to critical reviews of the literature by Hartwell (1) and Pusch (2) in as few as thirty-five cases is the diagnosis acceptable on the basis of adequately recorded histo-pathological evidence. In approximately three hundred reported cases, the foundation for the diagnosis rested on clinical grounds, including:

1—a positive Wassermann reaction, 2—favorable

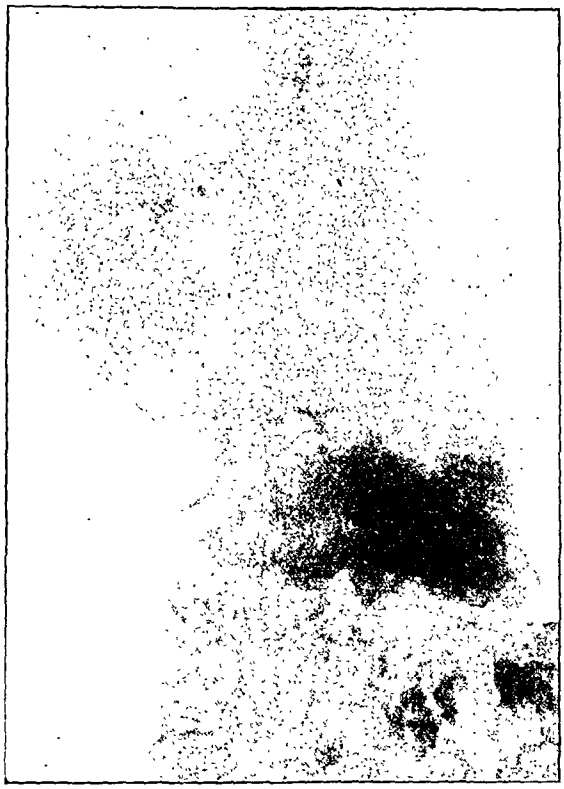


Fig. 1

response to anti-syphilitic therapy and 3—roentgenological simulation of either ulcer or carcinoma.

A review of the literature reveals that the diagnosis of gastric syphilis may be compatible with negative serologic reactions. In 7.5% of cases in the extensive series reported by Eusterman (3) the Wassermann was negative.

There may be, furthermore, in absence of symptomatic and/or roentgenologic improvement following application of therapeutic test no confirmation of clinical diagnosis. The condition of 29% of patients in this series of specifically treated cases was reported as being unchanged and 7% as having died (4). No roentgenologic change was observed in 46% of these patients re-examined with X-rays after anti-syphilitic treatment (5).

Rarity of morgue incidence is stressed by all contributors to the literature. Turnbull (6) of London, is quoted as finding a single possible case of luetic stomach in 3,000 necropsies. Symmers (7) at Bellevue in a study based upon 4,880 autopsies found among 314 syphilitics only one case of gastric involvement of a specific nature. Singer and Meyer (8) at Cook County did not find a single instance in 5,000 autopsies. The case to be described here is the second of its kind encountered by a local group of pathologists (9) in 15,000 postmortem examinations, covering an experience of 25 years.

A survey of the authenticated cases shows that frequently the diagnosis was unsuspected pre-operatively or antemortem, being fortuitously arrived at by the pathologist.

Although the serologic reactions in the case to be described were practically negative and the final response to intensive anti-luetic therapy indifferent, the clinical diagnosis was adhered to regardless of persistent roentgenologic hour-glass deformity simulating carcinoma (Fig. 1).

REPORT OF CASE

W. U. was a white man, 47 years of age, unmarried automobile salesman, whose chief complaints on first admission to Cedars of Lebanon Hospital, August 5, 1936, were epigastric distress, vomiting and loss of weight. Past history revealed luetic infection in 1917 which had been treated. Veterans' hospital records disclosed blood Wassermann and spinal fluid as negative in 1935. The onset was in 1933, when patient had pain-food-ease sequence and relief by alkalies. Symptoms during the year preceding entrance to hospital had been increasing in severity, patient experiencing epigastric discomfort described as a sensation of distension aggraved by solid food, emesis giving relief. Attacks were most severe after midnight. Large quantities of mucus were present, gross blood being seen on one occasion. Liquid was better tolerated than solid food. Alkalies, anti-spasmodics and hypnotics were ineffective in allaying distress. A loss of weight of thirty pounds was precipitated by a semi-starvation treatment (?) with colonic irrigations inflicted by a cultist institution. Physical examination showed a white man of good color, whose bodily nutrition was well maintained despite loss of weight. Resistance to palpation was encountered in the epigastrium but no tumor mass could be felt. Although the Romberg was negative, inequality of patellar reflexes was noted. Leucocyte counts ranged from 15,000 to 10,000, neutrophiles 73.5 to 80.5%, hemoglobin 89 to 93% and erythrocytes 4,800,000.



Fig. 2. Large superficial ulcer.



Fig. 3. Enormously thickened stomach wall, bisected and everted.

Stools were chemically positive for occult blood on two occasions and negative a like number of times. Investigation of hepatic function yielded a negative galactose tolerance test and an icterus index of 7. Gastric contents contained free HCl and gave positive guaiac tests. Two Wassermann reactions shortly before and after specific treatment was commenced were doubtfully positive, the Kahn precipitation test being negative. At the conclusion of fourteen weeks of antiluetic treatment, both Wassermann and Kahn tests were negative. An electrocardiogram showed slight elevation of T take-off in Leads I and II and an upright T wave in Lead IV, suggesting possible coronary artery involvement.

X-ray on August 7, 1936, showed a persistent hour-glass deformity (Fig. 1). On re-examination Sept. 5, roentgenologist reported infiltration was increased as compared with previous exposure. Serial refills of the stomach with barium at monthly intervals during the following eight weeks showed expansion of upper and lower loculi, hour-glass constriction of the midportion persisting. August 8, it was observed that patient's general condition did not correspond with the degree of carcinomatous involvement simulated by X-ray findings. In view of the luetic history although the Wassermann was doubtfully positive and the Kahn negative, a provisional diagnosis of syphilis of the stomach was made.

Patient was given daily intramuscular injections of 1/6 gr. mercury succinimide and 225 grains of sodium iodide, orally, for three weeks preliminary to neoarsphenamine. There was no amelioration in symptoms after five weeks of hospitalization. Although X-ray indicated increased infiltration and despite chiding from roentgenologist and others, patient was dismissed without surgical exploration. Since patient's body weight had been maintained, it was felt that ultimately he would respond favorably to further antisyphilitic treatment.

Additional treatment was given totaling 5 gr. mercury succinimide 3 Gm. neoarsphenamine and 24 gr. thio-bismol, along with sodium iodide. Three weeks after dismissal from hospital, patient had gained fifteen pounds in weight, showing definite symptomatic improvement.

An exacerbation of repeated attacks of emesis preceded by abdominal distress, (replacing epigastric discomfort), commenced October 9. Pain and emesis increased in severity during the ensuing month. A loss of five pounds in weight took place in the week preceding re-entry to hospital, patient reporting vomiting considerable quantity of bright blood on one occasion. Surgical exploration now seemed advisable, diagnosis on re-admission November 16 being gastric syphilis.

Operation was performed November 17 by Dr. Isaac Y. Olch. The stomach was found to contain a mass of enormously thickened or edematous inflammatory tissue extending across the middle. Above this mass of scar tissue the stomach was dilated resulting in a definite constriction or hour-glass deformity. Because of the extent of the edematous inflammatory tissue, it was impossible to excise scar. Gastro-enterostomy was done anteriorly. Following evisceration 11/30/36 patient died 12/4/36.

On postmortem examination was found a large superficial ulcer (Fig. 2), with a slightly rolled up edge covering about one-half the area of the open stomach, the wall of which was enormously thickened (Fig. 3). The induration extended along the lesser curvature practically to the esophageal opening, the base of the ulcer encircling the midportion of stomach being of firm fibrous tissue. The lining of the aorta was greatly roughened being raised into irregular folds (Fig. 4). In both lungs was an extensive consolidated bronchopneumonia with abscess formation. Microscopic section through the edge of stomach ulcer shows the enormous thickening, edema and dense fibrosis in the submucosa. The round cell infiltration is diffuse and extensive (Fig. 5). In sections of the aorta there was round cell infiltration about the vasa vasorum.

The pathological and roentgenologic findings in this case agree with the excellent description by Pusch (2). The thickening is concentric and sufficiently predominant between cardia and pylorus to result in hour-glass deformity. The annular involvement is primarily intramural with extensive secondary superficial ulceration.

As first observed in America by Flexner (10) the



Fig. 4. Gross appearance of syphilitic aortitis.

pathological process is localized chiefly in the submucosa. The ulcer is not gummatous but rather an indirect form of necrosis of mucous membrane brought about by combined softening of submucous infiltration and obliteration of blood vessels in the same situation. The mucous membrane thus deprived of its nutrition becomes necrotic, is removed, the ulceration resulting. As Boyd (11) points out, it is by no means easy to say even under the microscope if a piece of stomach wall is or is not syphilitic. The only adequate proof—that of sp. pallida has not been incontrovertibly offered.

Judged by existing pathological criteria, there is adequate anatomical evidence in this case to justify the diagnosis of syphilis of the stomach.

COMMENT

A laboratory finding which may bear only a chronological relationship was a gradual reduction in the leucocyte count from 15,000 to 10,000 accompanied by the disappearance of occult blood from stool. The neutrophile trend, however, was upwards. In any event, the preceding observation lent a bit of moral support to the differential diagnosis, the interpretation being that of a favorable response to treatment in a secondarily infected ulceration of a specific rather than a carcinomatous growth.

Carman's (12) observation in 1917 of the disproportion between patient's generally good condition and the extent of gastric involvement, roentgenologically simulating malignancy has been emphasized by many subsequent contributors to the literature. Even with this thought in mind, it was not easy at all times to maintain courage in adhering to diagnosis of gastric syphilis in the face of refractory response to what is ordinarily regarded as specific therapy in specific disease. Since the odds, statistically, favor the diagnosis of carcinoma, the consequences of mistaking a malignant for a syphilitic lesion are likely to be disastrous from a diagnostic standpoint. It is not surprising, therefore, that early surgical exploration has been recommended by internists and syphilologists as well as surgeons whenever the slightest suspicion of carcinoma is entertained.

In giving indications for laparotomy, Meyer and Singer (13) point out that it is generally agreed that only a relatively short period for the therapeutic test is warranted. Einhorn is quoted as recommending a test period of from two to four weeks. Bockus and Bank (14) quote O'Leary and Eusterman as regarding six weeks as the average time.

Stokes is cited as believing that six weeks is too long to wait when there is some chance for radical removal if prompt operation is performed. He recommends two injections of 0.3 Gm. of arsphenamine to be followed by operation if no improvement occurs.

In the writer's opinion the loss of time being the most serious objection to the therapeutic test in event the lesion proves to be carcinomatous is of little therapeutic significance. Either carcinoma or syphilis of

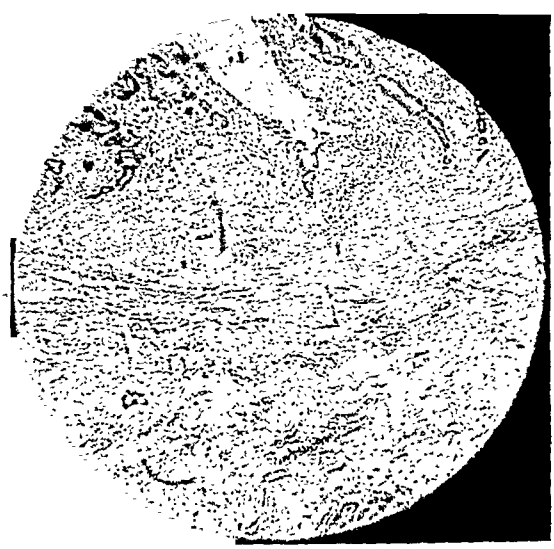


Fig. 5. Microphotograph of a section through the mucous membrane shown in Fig. 2. Cellular infiltration edema and hypertrophy of submucosa.

the stomach of a roentgenologic magnitude apparent in Fig. 1 on surgical exploration is likely to be found non-resectable.

SUMMARY

This case of gastric syphilis is reported because:

1. The diagnosis was confirmed by histo-pathological study.

2. The diagnosis may be compatible with (a) negative or weakly positive serologic reactions (b) failure of symptomatic and/or roentgenologic improvement after intensive antisyphilitic treatment.

3. It resembled late carcinoma therapeutically as well as roentgenologically insomuch as neither condition is amenable to treatment.

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Carcinoma of the Small Intestine as a Hidden Cause of Anemia

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and

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PRIMARY carcinoma of the small bowel is not frequently encountered. At the Mayo Clinic, of all the carcinoma of the gastro-intestinal tract, from the cardiac end of the stomach down to and including the rectum, only .62% are located in the small bowel (1).

The symptoms arising from carcinoma of the small intestine, as a rule, result from either obstruction or anemia. When obstructive features are present, a correct diagnosis is reached with little difficulty; however, when such a bowel or abdominal history is lacking, a resulting anemia may present a most puzzling diagnostic problem to the physician.

The following case report demonstrates: first, how baffling and intractable anemia and debility may be as a result of a concealed carcinoma of the ileum, and second, the remarkable absence of any abdominal findings or symptoms directly referable to an intestinal new growth, which had undoubtedly been present for many months.

The history of this patient about to be recited is involved. It will, however, be given in a somewhat detailed fashion in order that the reader may thoroughly evaluate the situation.

The patient, a woman, aged 54, first consulted us in regard to her present illness in May, 1934. At that time, her chief complaint was "spells of weakness and easy fatigue associated with distress over the heart." She had had what she called an attack of "Flu" three months previously, following which her heart palpitated on exertion, and she would tend to have short spells of sharp pains in her left chest. Following an attack of palpitation, she would be extremely weak and compelled to lie down. Her appetite was poor, with a resulting weight loss of twenty pounds during those three months. She was somewhat nauseated at times. The patient has had fever of 100° F frequently during the past few weeks with occasional sense of chilliness.

Hemorrhoidectomy had been carried out elsewhere two months previously. The first attempt in the surgical procedure had to be postponed because of severe pains in the back and through the chest, apparently coming on following the preoperative hypodermic. The operation was successfully performed two days after this episode, with subsequent satisfactory healing of the rectum.

Evaluation of the history brought out numerous minor complaints which were, however, of no significance in this record. An appendectomy and a Baldy-Webster suspension of the uterus was done in 1920. In 1922, several stones were removed from the gall bladder, and three years later a complete cholecystectomy was done. All of this surgery was carried out by us. Recovery from these surgical procedures was uneventful. Both tonsils were removed in 1925. Her health in general had been very good during the past few years.

Physical examination as noted at that first visit was as follows: Patient is a middle-aged, white female, who has apparently lost some weight and appears to be in poor general health. Temperature is 99° F. Pulse rate is 96 per minute. Respiration is 20 per minute. Blood pressure is 140/64, measured in millimeters of mercury. Her weight is 145 pounds. The skin has an ashy, grey, pasty appearance, and the mucous membrane suggest anemia. Hair, scalp, eyes, ears, nose are normal. The teeth, gums, and throat are in good condition. The thyroid gland is palpable, but not enlarged. No glands or stiffness of the neck can be found. Chest excursion is normal on each side. The breath sounds are normal. The apical heart beat

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Fig. 1. Photograph of gross specimen. Upper arrow is passing down ileum toward tumor and the lower arrow is situated in the distal ileum as it passes away from the tumor.

is heard best in the sixth interspace, 12 centimeters from the sternal border. The heart beat is forceful, and the second sound is accentuated over the entire precordium. No murmurs can be elicited. The muscles at several areas on the chest wall seem tender to firm pressure, and this is particularly noted posteriorly on either side of the sixth dorsal vertebrae. The back is otherwise normal. The abdomen is rounded and soft, and no tumors are found. There is a slight tenderness on deep palpation over the cecum and mid-epigastrium.

Examination of the pelvic organs shows the uterus to be of normal size and well-fixed anteriorly. The left ovary cannot be palpated; however, there is a small, firm, freely movable mass in the right adnexal region which is undoubtedly a somewhat enlarged ovary. The rectum shows considerable sensitivity and sphincter tone is more marked than usual. All deep tendon reflexes are exaggerated although no pathological responses can be demonstrated.

The patient had been seen and treated in the years past by one of us, for minor spells of easy fatigue, palpitation, and nervousness. The history at this time naturally suggested somewhat the same story that she had told us in those past years, for which an organic basis was never found. Because, however, of (1) fever, (2) weight loss, and (3) apparent general debility, it was felt that something organic must have appeared in order to produce those findings.

A period of hospitalization for more thorough study and observation of the patient was carried out with the following additional information. The patient consistently had an afternoon rise in temperature usually between 99° F. and 100° F. A catheterized specimen of urine showed a faint trace of albumen and 80 pus cells per cubic millimeter. Hemoglobin estimated by the Dare method was 83%. The red blood cells numbered 4,180,000; the white blood cells, 8,750 per cubic millimeter, and the morphological study of stained, differential blood smears did not show any points of significance. Inspection of the rectum showed one area of residual scars of recent surgery and several small internal hemorrhoids. A shallow fissure was found in the posterior commissure of the anal canal. Sigmoidoscopic examination was negative. A trace of occult blood was present in the fecal matter; however, this was while the patient was on a full diet, and this finding was not considered significant. During her hospital stay, the patient complained of numerous aches and pains throughout the chest, back, and abdomen, although none of these seemed to aid in interpreting her case. The temperature gradually resumed a normal level, the pulse maintained a normal rate, and she improved generally. Repeated examinations of the urine proved this difficulty to be subsiding. She was dismissed from the hospital after ten days in a much improved condition, and continued as an ambulatory patient on treatment for her (1) general health, (2) urinary infection, and (3) apparent nervous instability.

During the next three months, the patient remained considerably improved. Her appetite was fair and her bowels continued entirely regular. Her weight remained at 145 pounds. Her weakness was still noted and she occasionally had fleeting pains through the region of her heart, and noted palpitation on moderate exertion. She occasionally had mild gaseous indigestion after meals. The urine became normal.

The patient returned in September of that same year, four months after her first examination, complaining of a return of her general weakness and recurring afternoon fever averaging usually about 100° F. The gastro-intestinal tract remained symptomless. She slept well, had a fairly good appetite, and there was nothing in her history to arouse suspicion regarding the source of any trouble. The patient appeared to be more anemic. The pulse rate was 90 per minute. The blood pressure was 126/70 measured in millimeters of mercury. Her temperature was 99° F. Physical examination revealed no additional features. At this time her hemoglobin was 60% (Dare). The red blood cells numbered 3,480,000, and the white blood cells 13,300 per cubic millimeter. Study of the stained smears demonstrated considerable achromia and poikilocytosis of the erythrocytic elements. The urine showed 20 pus cells per cubic millimeter, but was otherwise normal. Analysis of the gastric contents after an Ewald meal demonstrated values for free hydrochloric acid 14, and total acid 32. An agglutination test for Malta fever was negative. X-ray visualization of the entire gastro-intestinal tract showed no pathology. Sigmoidoscopic examination was negative with the exception of the presence of an irritable rectal canal with small irregular internal hemorrhoids and small posterior fissure. Slight bleeding occurred in this fissure following instrumentation of the rectum and the patient stated she had noted a streak of red blood in the stool at times.

Our impression at the time of this second examination was that this patient's symptoms were due chiefly to her anemia which we felt was caused by her poor nutritional state and in part by slight rectal



Fig. 2. Metastatic nodule in liver tissue.

bleeding. During the remainder of the patient's life, the anemia was the outstanding feature, and our efforts were directed toward irradication of this problem. The rectum was treated locally, and she was given strenuous anti-anemic therapy.

Some symptomatic improvement resulted in the following few weeks; however, there was a tendency at times to note palpitation, shortness of breath, weakness, and pains over the heart on slight exertion. In spite of many weeks of anti-anemic therapy and conservative therapy for her rectum, only slight improvement was noted in her anemia. The urine remained free from significant amounts of pus. A low grade afternoon fever continued quite regularly and her general debility constantly was prominent. The patient noted frequently a vague sense of fullness and deep dull distress in the right upper abdomen. Anemia was the only satisfactory explanation we were able to give for any of these subjective symptoms. Her condition remained unsatisfactory, but there were times when the patient felt considerably stronger. We were at a loss to know what was causing the patient's anemia and *why* it did not respond to numerous schedules of stringent blood building therapy.

In the early months of 1935 we continued attempting to build up the patient's general health through every possible route. In spite of our efforts, examination of her blood in May showed 62% (Dare) hemoglobin and the red blood cells numbered 3,200,000 per cubic millimeter. Marked achromia, anisocytosis, and poikilocytosis were present with numerous macrocytes. We never were able to find a nucleated red cell in any of her blood smears. A trace of occult blood continued to be present in the stools; however, this feature was again discounted because of her general diet, liver preparations, and possible occasional drop of blood from the rectum. The slight right ovarian enlargement remained unchanged in size or character.

We had been handling this patient for ten months and were unable to improve the anemia or find the cause of the trouble, so our suggestion at this time was that the patient have a complete examination by another consultant; and this course was immediately followed.

This investigation resulted in a negative report with the exception of the marked secondary anemia and a finding of blood in the stools. No note was made regarding the small tumor which we had found in her right pelvis. This consultant suggested that further rectal surgery be carried out in the belief that this was the source of her bleeding. This examination concluded a very complete laboratory and Roentgen examination; and we were all again unable to find what we constantly suspected: a malignant growth.

Strenuous anti-anemic therapy was continued and every effort made to increase the patient's general physical state. She was anxious to visit relatives who lived in the lake section of Wisconsin and this trip was advised in hopes that such a rest would further increase her general health. She was followed closely by a physician in that locality who promptly reported back that the patient was not improving. In fact, the anemia and general weakness became more pronounced.

She was advised to consult another clinic group at once; and on August 29, 1935, the patient presented herself to that group for a thorough investigation. Here again an attempt was made to explain the weakness, physical and mental depression, fever and anemia. They verified the findings of a firm, possibly cystic, moveable mass in the right side of the pelvis, which they also thought probably ovarian, since it could not be localized through X-ray examination of the stomach, colon and sigmoidoscopic examination for a distance of 24 centimeters. These consultants did advise the patient to remain for a motor meal in order to investigate particularly the ileocecal coil, however the patient refused this re-check. This clinic group might have identified the tumor, had such a procedure been carried out. Their only suggestions were to continue liver and iron therapy and to have periodic examinations of the tumor in the pelvis. Finding a trace of occult blood in stools was not considered of prime importance.

The patient returned home and seemed to show a slight improvement. She became afebrile and her strength was definitely better. We repeatedly examined the pelvis in regard to the right pelvic tumor and made a note that it had remained unchanged since our first examination over a year ago, and that the tumor was undoubtedly ovarian and of no real significance. We also appreciated the fact that previous pelvic surgery might have distorted the pelvic anatomy.

Improvement was only temporary and her condition again began to fail. Because of the extreme seriousness of her condition and our utter inability to either make a diagnosis or to successfully treat her, she was advised to consult still further.

In October, 1935, she visited another consulting physician who again carried out a thorough investigation, the results of which gave us no additional findings. This physician felt the anemia belonged to the so-called hypochromic type, and his only suggestion was to continue with iron and liver therapy. Again the possibility of a malignant growth seemed to be ruled out.

The patient's condition gradually became more severe and constant bed rest became a necessity.

In November, 1935, she was again hospitalized by us for the purpose of giving her repeated blood transfusions combined with a regime of absolute bed rest. Examination again revealed a severe secondary anemia and a constant daily fever of between 100° and 101° F. Hemoglobin was estimated to be 50% (Dare). Red blood cells numbered 3,280,000 per cubic millimeter. The only other finding which we previously had always noted was the presence of small amounts of blood in the stools. The abdomen was entirely negative to examination and the bowels were very regular. The patient did complain from time to time of vague upper abdominal symptoms and nausea. However, we could place no significance to these features. During the course of six weeks, blood was given intravenously and intramuscularly at frequent intervals to a total of 1780 cubic centimeters. Liver and iron was administered by intramuscular injection. A re-check of her gastric analysis showed a comparatively low amount of free hydrochloric acid, so this acid was supplied with each meal with a resulting lessening of her nausea. Considerable improvement was evidenced during the first weeks of this hospitalization, and her hemoglobin was elevated to 70% (Dare) and the red blood cells numbered 3,790,000 per cubic millimeter. She continued to show a mild leukocytosis, however the morphology of the white cells remained normal. Her condition in general was the best it had been for several months and her temperature only occasionally reached 99.4. She was again sent home on a restricted schedule of activity and a continuation of anti-anemic and general measures. This improvement was of relatively short duration, and she promptly showed a return of her severe anemia, fever and extreme weakness.

Our impression was that this was either a malignancy which we were unable to identify; or, it was a primary blood disease which was not amenable to any therapy which we had to offer. We were at a complete loss to know what next to do. We had repeatedly considered the advisability of performing an exploratory abdominal laparotomy; however, it seemed useless to enter an abdomen which neither history or clinical findings could point to even a suspicious organ. We were convinced that the small pelvic tumor was an innocent, right ovarian enlargement. We advised bed rest at home, liver, iron, sedatives when nervous, vitamines and a nourishing diet. She continued to fail; and during the last week of her illness, her weakness, weight loss, and general debility was most marked. She veritably melted away under our own eyes and we were ignorant of the cause. During the last few days of her illness the fever was extreme and her pulse was practically imperceptible. Twenty-four hours before her death, the patient expelled a large, liquid, bloody stool. This was not of the tarry type, however it was not bright red. This hemorrhage convinced us that she had a tumor of the bowel as the chief cause of death which we knew must inevitably follow in a few hours. Death occurred on April 13, 1936, over two years following the onset of her illness.

POST-MORTEM REPORT

The autopsy was performed at a funeral home eight hours post-mortem.

The body is that of a white female, apparently about fifty-five years of age. There has been marked weight loss and there is a marked pallor to the skin and mucous membranes. Old upper, right rectus and lower, mid-line abdominal surgical scars are present. The eyes, nose, ears, and mouth are essentially negative. Nothing of note is evidenced on the extremities other than emaciation and pallor.

A "Y" type autopsy incision is made, exposing the thoracic and abdominal cavities.

The Thoracic Cavity: The pericardial sac is normal in size, shape, and position, and contains about five cubic centimeters of clear, straw-colored fluid. No adhesions are present. Both pleural cavities are free and contain no excess fluid. There is considerable hypostatic congestion, but no true consolidation is present. The diaphragm is in a normal position on both sides. Mediastinal contents and hilus glands show nothing of note.

The Abdominal Cavity: The solid organs are in normal position and nothing unusual can be seen on superficial examination of the abdominal contents. There are dense adhesions in the region of the gall bladder fossa which fix the duodenum and hepatic flexure of the colon firmly against the undersurface of the liver. The appendix is absent. The cecum is free. Many enlarged lymph glands are present medial to the cecum, representing a marked lymphadenopathy of the mesenteric and retroperitoneal chain of nodes. These glands extend up along the root of the mesentery to the pancreas. The largest node measures 2 x 2 x 3 cm. Evidence of surgical uterine suspension is present which holds a small regular uterus anterior in good position. The right posterior part of the fundus



Fig. 3. Portion of small nodule found in wall of jejunum. The jejunal mucosa is not related to the tumor nodule.

is adherent to a fixed, firm, tumor mass in the right pelvis, which at first seems to be a right ovarian tumor. This, however, proves to be primarily in the small bowel and has no connection with the right tube or ovary which are normal and free. The left tube and ovary are also normal. One loop of small bowel is plastered down around this mass; however, it can be freed fairly easily. The involved ileum is intimately associated with the mass; and in order to facilitate this part of the examination, the ileum is well resected from the ileocecal valve. This bowel is traced directly into the pelvis for a distance of about twelve cm. where it is then found to be apparently a part of the tumor. An resection is made at this point. The wall of an abscess is broken, allowing the escape of a greenish-yellow, purulent material measuring about fifty cubic centimeters. The remainder of the tumor, as it passes to the rectum, is intimately associated with the rectum; but it does not appear to be the primary source of the pathology. The entire mass, with the sigmoid colon and female organs, is resected en bloc, and will be more completely described later.

Bowel: There is no change of significance to be found in the colon.

Lungs: Not any of the large examples of the lower lobes. No gross evidence of pneumonia is present. Multiple small nodules of tumor are present throughout the lungs, especially at the bases.

Spleen: The spleen is slightly larger than normal, and is pale. On the anterior surface of the left lobe is found a small, hemispherical, encapsulated mass, one centimeter in diameter, beneath which is a tiny infarct. On cutting this mass it is found to measure two centimeters in diameter, is white in color, and quite friable. The trabeculæ of the nodule are sharply demarcated from the liver substance. No capsule is present. On microscopic section of the nodule of the liver, only liver cells are found. There is one small nodule, located deeply in the right lobe, measuring one centimeter in diameter, and has the same gross appearance as the larger tumor. The liver substance on cut section has a marked "nutmeg" appearance.

Gall Passages: The common duct is of normal size and the hepatic ducts are patent throughout. The gall bladder and cystic duct have been removed previously.

Pancreas: The pancreas and duodenum are normal.

Small Bowel: Careful inspection of the small intestine from duodenum to mass in jejunum reveals only one point of interest. This is a small firm, fibrous nodule, measuring eight millimeters in diameter, and located in the intestinal wall of the jejunum about eight centimeters from the duodenum. Cut section of this nodule points to the probability that this tumor is not connected with the mucosa or serosa. The cut surface is white, granular, and semi-firm. On microscopic examination, this appears to be an adenoma of the jejunum.

The pancreas is normal.

Spleen: The spleen is about twice normal size. The capsule is of a bluish-black color and seems quite tense. The pulp, on section, is dark and friable. No nodules are present.

The kidneys are essentially negative. The cut surface is pale.

The adrenals are negative.

The female organs are negative except as noted elsewhere.

The urinary bladder and ureters are normal. A small amount of cloudy urine is present.

The above described pelvic mass is removed *in toto*, along with the uterus, ovaries, tubes and sigmoid colon. Careful dissection of this mass shows it to be made up primarily of a polypoid tumor involving eight centimeters of the ileum. The site of the original tumor is about fifteen centimeters from the ileocecal valve. The tumor mass has perforated and allowed an abscess and inflammatory reaction to surround this loop of ileum. Because of its size and obstructive nature, it is impossible to see grossly how even liquid bowel content could pass by the tumor without considerable difficulty (Figure 1). The entire mass measures about five centimeters in diameter. Soft, fluid fecal matter is present throughout the colon and lower ileum. The lymph nodes, on section, are white in color; the cut edge is fairly sharp, and there is a softening and friability associated with the central portions of several nodes.

Microscopic study of tissue from this case demonstrated that the lesion of the ileum was an adenocarcinoma (Figure 2), and the same type of new growth was found to make up the mesenteric lymphadenopathy and liver nodules. Section of the small jejunal tumor revealed this to be a small clump of normal appearing glandular structures (Figure 3). The exact nature of this tissue nodule is problematical, however, it seems unrelated to the malignant tissues, and may represent a nest of heterotopic pancreatic cells. There was marked fatty degeneration of the liver, and considerable cloudy swelling of kidney parenchyma. The spleen pulp was engorged and the lymph structures of these organs was hyperplastic.

COMPLETE PATHOLOGICAL DIAGNOSIS

1. Adenocarcinoma of the ileum (perforating and hemorrhagic in nature).
2. Metastatic carcinoma of sentinal lymph nodes and liver.
3. Small adenoma of jejunum (pancreatic cells).
4. Parenchymatous changes in liver and kidneys.
5. Emaciation.
6. (Previous surgery) Cholecystectomy, appendectomy, and Baldy-Webster suspension of the uterus.

DISCUSSION

In spite of what we felt were continued determined efforts to establish a diagnosis in this case, the lesion which had been gradually squeezing out life remained completely hidden until two days before death, when a massive block stool spelled cancer of the bowel. The features of progressive anemia, debility, and fever could not be explained, and furthermore, failed to respond to any treatment.

It is just this point which has been stressed of recent months by several authors, and we wish to again call it to the attention of our medical group. In any case of unexplained debility and anemia, a hidden carcinoma of the small bowel is quite possible.

This brings us to face our first criticism: more repeated efforts should have been made to visualize the small bowel by newer radiological diagnostic methods. In previous years, the major part of the small bowel has been considered quite impossible to visualize. This conception has changed to the point that, as Weber states: (1) "the roentgenologic examination con-

scientiously and properly performed can be made to be quite as accurate and reliable in the diagnosis of diseases of the small intestine, as it has become in the diagnosis of diseases of the esophagus, stomach and colon."

The second criticism we offer is that an early exploratory surgical procedure should have been carried out, in which case at least the hemorrhaging lesion could have been readily removed, even though a cancer cure might not have been possible. Such a procedure might have added years to this patient's life, and if done early enough, would have carried possibility for complete cure. We hope through this report to stress these two criticisms and offer them as urgent suggestions to those doctors who may see such rather rare clinical problems as the one recited.

SUMMARY

1. A case of carcinoma o the ileum is presented.
2. Continuous slight bleeding of a hidden small intestinal carcinoma may produce "unexplained anemia."
3. More careful roentgenological examination of the small bowel is urged in cases of suspected gastro-intestinal bleeding.
4. Laparotomy may be the only means of discovering a bleeding carcinoma of the small intestine.

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Errors in Gastro-enterologic Diagnosis

By

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AFTER many years of gastro-enterologic practice I am convinced that success in this field rests largely on the ability to make a correct diagnosis. This is, of course, to a certain extent true of all other branches of medical art, but in the gastro-intestinal field as in no other, is the available information so equivocal, even though we have the fullest cooperation from the patient. And it may very well be added, in no other field are mistakes in diagnosis so serious in their immediate consequences, nor so far-reaching in their ultimate results.

The psychology of the gastro-intestinal patient is peculiar. It would seem that the majority of those who are referred after their ailments have become well-established visit the consultant not so much to find out what he thinks, as to judge of that doctor's cleverness and professional acumen, by concealing from him all the data which they alone can supply, as if to see if he still can make a diagnosis in spite of all the hindrances they can possibly throw in his way. Some will volunteer no information — it must be drawn from them by prolonged and searching questioning. Others wilfully conceal their symptoms. Others again will greatly magnify their ailments, or will minimize them by gross understatement. Frequently — in clinic practice especially, the patient will be unable to command language in which to describe what he has felt. Or again he may be so hypersensitive to suffering of any kind that all his statements must have allowance for exaggeration. Or he may be so insensitive that he pays little attention to suffering that would unnerve one less phlegmatic in character.

It was of such material that Alexander Moore (1) must have been thinking when he wrote: "Mistakes in diagnosis are of three kinds: (1) the diagnosis of a lesion is made when disease is not present, a wrong affirmative diagnosis. (2) Disease is present but is not discovered, a wrong negative diagnosis, and (3) a lesion is found but is not properly identified, a wrong differential diagnosis." Thus is set forth, in one terse paragraph, a whole chapter in modern medicine.

A surprisingly large number of patients come to our clinic bearing with them X-rays taken elsewhere, accompanied by fanciful diagnoses which very likely bear no relation to either the physical findings on entrance, or the correct reading of the roentgenographs supplied. All too frequently commercialism enters in to influence the interpretation of the X-ray pictures. The physician who first examines the patient decides what symptoms and history indicate, and refers his patient to a roentgenologist — not for independent and unbiased examination, but for a *confirmation* of his findings.

Very often we find that the original roentgenograms led to an erroneous diagnosis because of spastic phenomena which may be present from a number of different causes. The skilled roentgenologist will allow for possible spasm, and the experienced gastro-enterologist may even be assisted in making his diagnosis because of the existence of a spastic condition is confirmation of certain pathologic conditions which may previously have only been surmised. But with a roentgenologist lacking in special knowledge of the behavior — normal and abnormal — of the gastro-intestinal tract; and a so-called gastro-enterologist who fails to make his own interpretation of the X-ray findings, after taking into consideration all the other data he has been able to obtain by physical examination, laboratory findings, and a searching inquiry as to the past medical history — the chance of arriving at an accurate diagnosis is very small indeed (2).

"High pressure salesmanship" has induced many physicians, who have no special training nor inclination for gastro-enterologic work to enter this field because a fluoroscope or X-ray outfit was presented to them so alluringly that it seemed a very easy way of becoming a "specialist," with a more leisurely life and larger emolliments which are *supposed* to accompany specialization. Is it much wonder that such

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grave mistakes continually occur in making diagnoses under such conditions?

An example of such errors is offered by three cases which came under observation following a negative roentgenographic report, reached because the gastric examination had shown no filling defect nor six-hour residue. Yet the chemical analysis done later revealed a true malignant achylia with unusually rapid emptying, while another Roentgen study showed a gaping pylorus and rugae largely effaced. In all three cases the sedimentation rate was found to be greatly increased. If these laboratory procedures had been done *before* the Roentgen study, how different might the interpretation have been!

As it was, reconsideration of all data led, in two cases, to a final diagnosis of infiltrating carcinoma of the posterior stomach wall, while the third proved to be a case of linitis plastica. There is a practical lesson to be learned here: Never accept a negative X-ray finding as final unless it is fortified by concurring clinical and laboratory findings. In gastro-enterology, as Koch said of tuberculosis, "Absence of proof is no proof of absence."

FAILURE TO IDENTIFY LESION

We now come to Moore's third postulant: The lesion is found but is not properly identified. A phlegmatic individual presented a clinical picture which was not in most respects characteristic of the silently bleeding duodenal ulcer which operation later revealed. The pre-operative diagnosis was hypochromic anemia. The X-ray report was negative for both pre-pyloric and post-pyloric ulcer. Gastric chemistry recorded high acid values, and occult blood was detected in the stool. The operation revealed a small lesion on the posterior wall of the duodenum, with a shallow crater incapable of retaining a central fleck of barium. X-ray had also failed to show the duodenitis — precursor of ulceration — which might have helped in the pre-operative recognition.

WRONG DIAGNOSIS DUE TO IMPROPER ROENTGEN TECHNIQUE

Among the great quantity of roentgenograms which are brought to our clinic by patients referred from outside sources, there are but few which are technically adequate, or have any real diagnostic value. Not only is the photography itself poor; the entire procedure would appear to have been carried out with the idea of making as much commercial profit as possible for the roentgenologist, without regard to the needs of the physician who is attempting to make the diagnosis from these X-rays, or to the benefits which the unfortunate patient — who must foot the bill — hopes to derive from undergoing the ordeal of being roentgenologically examined.

The dorso-ventral position seems to be the only one most commercial X-ray men are aware of. They pay no attention to the body habitus of the particular individual under observation, and as a result, bony landmarks are not uncommonly wholly beyond recognition. Again and again the very viscus which is supposed to be under examination will be partially or even wholly invisible. Most of these "sets" of gastro-intestinal tract roentgenograms consists merely of 24-hour observations following the ingestion of the barium meal. It is quite impossible to ascertain the rate of colonic motility in a period of this length. Seldom is the necessary information in regard to the condition of the appendix elicited. No attention is paid to its filling time, to whether or not emptying is delayed, whether it is freely moveable, or is fixed by adhesions, and practically never is there any attempt to palpate the appendix under screen observation in order to see if tenderness can be elicited. Yet no gastro-intestinal examination is complete if no attempt has been made to gain this information.

Not only is the motility of the appendix passed over as of no importance; the movements of the colon itself are seldom routinely observed and recorded. Roentgenography, without collateral roentgenoscopy, is of small value for gastro-intestinal diagnosis, for the "mechanics of the digestive tract" are of equal, if not greater importance than its outlines, or the density of its shadows. Only those who have had both bedside and laboratory experience, who have seen these conditions many times not only in the clinic but at the postmortem table as well, are competent to interpret radiograms, or to make them in the first place. Merely owning an X-ray machine does not supply a man with such knowledge, any more than the possession of a rapier makes him an expert swordsman. The family physician who has equipped himself with a fluoroscope has not by such a purchase automatically become an expert radiodiagnostician. Yet it is this type of ameteur work which we find everywhere in the gastro-intestinal field at the present time. To quote an able editorial by Burrill B. Crohn (3): "To let an inexperienced radiographer attempt the diagnosis of gastro-intestinal diseases is, unfortunately, only a waste of the patient's money and time, and a source of error to the family physician." The following is a case in point:

A woman 42 years of age, complained of diarrhea of several months' duration. Her family physician administered an opaque meal, fluoroscoped her and pronounced the stomach normal. The too-rapid emptying of the stomach was attributed to a 'neurosis,' and remedial medication given in the form of a bismuth salt powder. The remains of the barium meal and the bismuth salt combined to cause a partial obstruction of the intestine. After the lapse of several weeks another roentgen examination was made — this time with a flat plate. This showed barium still retained above an obstruction at the recto-sigmoidal junction. Proctoscopy revealed a cauliflower mass at this point. Had proctoscopy been done at the first complaint — as it probably would have been done had not the physician first consulted happened to possess a fluoroscope, although he was not equipped to do an instrumental examination of the rectum — much invaluable time would have been saved, and a fatal termination delayed, or avoided entirely.

When one considers what valuable information properly done radioscopy *can* convey, the failure to employ this diagnostic aid in the right way becomes little short of a crime against society. By no other means can we study the degree of pliability of the stomach wall, nor ascertain so well the function of the pyloric muscle; nothing else shows us the motility of the entire gastro-intestinal tract, how the viscera are separated, or how the terminal loop of the ileum lies in relation to the position of the cecum — a most important detail — knowledge which only the fluoroscope can supply. Palpation under the fluoroscope tells where tenderness exists deep in the abdominal cavity, and by changing the direction of the rays, and shift-

ing the position of the patient we can get views at practically all angles — an inestimable advantage.

Of course there are drawbacks and circumstances which lead to confusion, especially if the fluoroscopic examination is not backed up by flat roentgenography, and searching physical examination. As an example of this, Ettinger and Davis (4) have remarked, "Two circumstances make the fluoroscopic diagnosis of a niche extremely difficult for the roentgenologist. One of them is the great irritability of a diseased cap, which may be so marked that the actual time for perception of the silhoutte of the cap will be too short to recognize any details. A quick snapshot, however, makes a record which may be studied and evaluated later. Secondly, while usually the niche is represented as an area of increased density, swelling of the mucosa may obstruct the entrance to its lumen so much that only a slight trace of barium covers the base of the niche, and only a very faint shadow of the niche results, which escapes detection by fluoroscopy."

Still another consideration, is the danger of overexposure of the patient to the roentgen rays. We frequently dare not apply the rays long enough to enable us to visualize and examine suspected departures from normal outline and function. Combining fluoroscopic examination with the exposure of serial films lessens the chance of diagnostic error, by giving us data for counter-checking, and permitting us an opportunity to confirm by a leisurely examination of the films, the impressions gathered by fluoroscopic inspection.

CASE REPORTS ILLUSTRATING ERRORS

A history of several months' duration, obtained in the Gastro-enterological Department of the New York Medical College and Flower Hospital, from a man of 31 years, was generally vague, and in no way suggestive of ulcer, either above or below the pylorus. The gastro-intestinal X-ray series which he brought with him showed several plates in which the cap was not smoothly outlined. Presumably, because the bulb silhouette was not completely filled in, the roentgenologist had interpreted the irregular contour as indicating the presence of a duodenal ulcer. Yet chemical analysis of the stomach secretions produced acid values much too low for duodenal ulcer. Upon close study of the X-ray films a serrated appearance was noted in the outline of the greater curvature which may well have been attributed by the physician to indentation of the substance of the lower pole of the stomach by gas present in the transverse colon. Had the colon been properly cleared out before the X-ray exposures were made — a preparatory measure which should *never* be omitted, all such mistakes would have been obviated. Actually, the serrated appearance was caused by a large carcinoma arising from the greater curvature of the stomach. This was found at laparotomy to be inoperable because of metastasis to adjacent viscera.

Another case illustrates the folly of depending solely upon fluoroscopy in making a diagnosis of gastro-intestinal lesions: A woman in her late sixties showed a 6-hour residue on fluoroscopy of the barium meal. This was considered sufficient basis for a daignosis of gastric cancer. Another physician who examined this patient was interested only in the cardio-vascular system, and pronounced the case one of myocardial insufficiency. Circulatory failure soon brought about a fatal termination. A chronic gastritis, secondary to functional disarrangement of the circulation, had produced symptoms referable to the gastro-intestinal tract. The gastric symptoms occupied the high light in the clinical picture, obscuring the basic cause, and making the first clinician who examined the patient quite overlook the myocardial decompensation. Had X-ray films been available for leisurely examination, the absence of a filling defect would have been a complete negation of the diagnosis of carcinoma. The clinician would then, in all probability have bethought himself that a chronic pulmonary emphysema, with the myocardial weakness it can bring about, often causes a passive congestive gastritis so severe and to give rise to duodenal bleeding and ulceration. So, had fluoroscopy been combined with roentgenography, the symptoms of gastric distress, vomiting, etc., would have been recognized as cardiopathic instead of being primary to the gastro-intestinal tract, and the diagnosis of circulatory failure would have been readily reached.

Inadequate technique and improper interpretation of gastro-intestinal roentgenograms reach their acme when pathology of the appendix is in question. In the greater number of patients referred to our clinic, who come bearing their X-rays with them, the roentgenographic diagnosis will contain some reference to the appendix as a probable seat of trouble. Not a few patients come *after* they have been relieved of their appendices, but not of the symptoms which were previously attributed to disease of this portion of the intestinal canal. Many more bring a negative diagnosis, because the pictures made of them either did not show the appendix at all, or showed no drainage from it, or again, the films yielded no signs of the appendix but did reveal evidences which had been taken to indicate that the ileo-cecal valve was incompetent. The diagnosis of chronic appendicitis was usually based on visualization of the organ 24-hours after the barium meal was ingested; that of valve incompentancy on the visualization of a barium suspension enema — which is in itself an artifically induced incompentancy. No 24-hour examination can include proper study to determine incomplete filling, delayed emptying, and fixation of the appendix. To do this properly would mean continual observation until all barium had been emptied from the colon. And so long as the cecum and the ascending colon are still filled with the barium residue the appendix cannot empty because of regurgitation. Only when the proximal colon is empty, a cathartic having been used to insure complete voiding, if palpation under the fluoroscope still elicits tenderness, can we say positively that the appendix is at fault.

In respect to ileo-cecal incompetency — the readings taken before coming to us were invariably made from a suspension enema picture made *before* the medium had been evacuated. Most of the plates did not show the mucosal relief of the colon following the expulsion of a greater part of the enema material. No attempt was ever made to check the roentgenographic findings by those of the laboratory. For example, in true ileo-cecal incompetency indicanuria is common. When analyses were made of the urine of patients referred with this diagnosis indicanuria was not demonstrated. Such an examination, made before the X-ray series is undertaken, will serve as an important check, and help solve many diagnostic enigmas.

ERRORS IN INTERPRETING GASTRO-DUODENAL DISEASES

The factors of error in the diagnosis of gastro-duodenal disease made by X-ray alone have been well summed up by Kirklin (5) (in part): Failure to make due allowance for normal variants, or to exclude conditions simulating disease; reliance on secondary and indirect phenomena, and on a limited roentgeno-

graphic examination. My own experience supplies many examples of this first postulant. Ignoring the possibility of a spastic condition being present in the alimentary canal is probably the prime cause. Spasm is normal in certain parts and under certain conditions. Pathologic circumstances may arise which convert this normal spasm into most abnormal activity. Yet this is in a measure offset by the fact that not a few pathologic conditions betray their presence by evoking abnormal spascity. Very often it is the secondary and indirect phenomena which the competent and alert roentgenologist will observe and analyze which make diagnosis possible. But the X-ray is a machine, and most of those who employ it alone turn out machine-made results, varying the formula so little that one can usually foretell precisely what they have written down, even before unfolding the reports. All too many physicians, otherwise conscientious, have come to regard X-ray as a short cut to diagnosis and are willing to accept as gospel whatever interpretation a roentgenologist, often grossly deficient in the special knowledge required for proper deductions from the films of the barium-filled gastro-intestinal tract, may report the findings to be.

PROPER AND IMPROPER METHODS OF COLON ROENTGENOGRAPHY

Though there are many errors possible in examining the colon the most common are (1) Using roentgenography without invoking the aid of a fluoroscopic screen study, and (2) relying on a morphology plate alone, without seeking graphic evidence by inspection of the mucosa in relief, after the opaque medium has been evacuated from the colon. A competent internist, using his gloved hand, may with the aid of the fluoroscopic screen, view spastic phenomena with the naked eye, turning his patient from side to side until the whole digestive apparatus above the large bowel has yielded up its pathologic secrets.

Yet in such an examination diverticuli may be missed entirely, and ileo-cecal incompetency also. When studying the barium enema — if the first plate taken does not show the terminal ileum's outline, but the evacuation plate does show it, we may deduce a reflux from the cecum into the ileum; that is, ileocecal incompetency. The same deduction is justified when at the ninth or twelfth hour after ingestion of the barium meal, the ileum is empty, but when viewed at the end of the twenty-fourth hour, is found to be filled again. This too, indicates incompetency of the ileo-cecal valve.

DETECTING DIVERTICULI

Diverticuli can best be detected when the colon has been emptied of the barium, and one is able to view mucosa in relief only when the suspension enema has been completely withdrawn. Remembering that a colon may be morphologically normal, yet physiologically abnormal, it will readily be understood that either fluoroscopy or X-ray photography will fail to demonstrate everything, so that only by a combination of the two methods can we hope to discover both anatomical distortions and physiological disturbances. In one case which came under my inspection, a diverticulosis of the distal colon had been missed entirely, and was only brought to light when the double contrast method had been employed.

CO-RELATION OF ROENTGENOGRAPHY AND PHYSICAL FINDINGS

A roentgenographic diagnosis may be absolutely correct, yet if taken without consideration of the physical findings, absolutely misleading. This is illustrated by the case of a woman reported to be suffering from rectal constipation. Bi-manual pelvic examination, however, disclosed a cause, not only for the constipation, but also for the headache, backache and other symptoms for which the constipation — itself no more than a symptom — had been held responsible.

Relaxation of the recti muscles and extensive perineal tears involving the levatores ani were revealed by the pelvic examination. These were first remedied by suitable operative procedures. The supposed gastro-intestinal tract symptoms then disappeared.

X-RAY DIAGNOSIS OF GALL BLADDER DISEASE

"Mechanical cholecystography" accounts for many errors in the popular procedure for the diagnosis of gall bladder disease. How often is the patient questioned as to what has happened after he ingested the dye, but *before* the roentgenographic exposures were made? Even a slight diarrhea may be sufficient to carry off the dye before it could collect in the gall bladder densely enough to permit visualization. Knowing nothing of this, the roentgenographer will be unable to visualize the gall bladder, so will send in a report that the dye has not filled the gall bladder, making the findings 'positive' for a pathologic condition.

PROPER METHOD OF VISUALIZING THE GALL BLADDER

But when such a patient is given a mixture of opium, bismuth subnitrate and mistura creta in appropriate doses, he will sleep through the night and retain the dye long enough to permit its absorption in the gall bladder. Then if he undergoes a second X-ray examination, his gall bladder will be reasonably well visualized.

In two other cases where nothing could at first be made out of the gall bladder, it was noted that biliary drainage brought away only an oily material. This was due to the existence of cystic-duct catarrh. When this had been evacuated the gall bladder could be visualized, although rather faintly.

BILIARY DRAINAGE BEFORE ROENTGENOGRAPHY ESSENTIAL

The bile should always be examined before roentgenography is undertaken. If this is properly done biliary drainage will frequently furnish all the information required. This will spare both physician and patient additional trouble and expense.

Very frequently the outline of the gall bladder may be normal, but disease, nevertheless, will be present. More than this, drainage of the gall bladder is necessary before an X-ray examination is made if for no other reason than to fill the viscus with fresh bile, which entering laden with the dye, will give a sharp contrast such as stale bile will never offer. In some cases we cannot find out why the gall bladder does not show up on the X-ray film. But the routine of drain-

age and trans-duodenal lavage alone, was sufficient to clear up the pathologic condition — even if it never was adequately diagnosed.

Mention has been made of the importance of stomach chemistry in throwing light in otherwise obscure diagnostic factors. It is unfortunate that this valuable assistant to gastro-intestinal practice is not more widely employed. When rapid gastric clearance is seen under the screen its meaning may be wholly misinterpreted, unless it is checked up by the findings of gastric chemistry. In an elderly individual, rapid gastric clearance *may* mean a gaping pylorus — sometimes due to syphilis, but more often to a developing malignancy. Yet unaided the roentgenologist would report such a stomach as 'negative' to both these conditions. At best the screen only records motor function; chemical analysis tells of secretory activity — or the lack of it — which is just exactly as essential to adequate and complete diagnosis of gastric disturbance. The appendix may fill and empty normally, yet heightened gastric chemistry may throw an entirely different light upon the X-ray findings. A 'silent' duodenal ulcer may remain undiscovered unless persistent hyperchlorhydria, which Moynihan (6) has called "the term for the surgical condition of duodenal ulcer," is revealed by a chemical examination.

Gastroptosis, the "dropped stomach" of lay parlance, is the cover under which many an inefficient diagnostician — roentgenographic and clinical — has taken refuge. The number of patients who, having undergone operation, return with a diagnosis of "adhesions" would be a cause for laughter, were it not fraught with such tragic possibilities. Far more often the diagnosis should be "poor surgery" or "inadequate roentgenography." To quote Kirklin again: "On the roentgenologist devolves a two-fold duty: to find evidence of disease when disease is present, and to avoid a diagnosis of disease when disease is absent." It is harder *not* to find disease because of an inclination on the part of most examiners "to interpret all unusual phenomena in terms of pathologic change."

The economic embarrassment now burdening the rank and file of the medical profession appears to me to be the underlying cause of much of the demoralization now prevalent in gastro-intestinal diagnosis. In trying to make good the tremendous losses which all have incurred by the utter inability of perfectly honest patients to meet their financial obligations, many have been misled by specious arguments and attractive advertising into believing that it will be a relatively simple matter to "specialize" in roentgenographic diagnosis. Many a naturally analytical mind has thus been converted into a machine-made diagnostician. It is but evidence that physicians are primarily human beings; that they try to obtain a share of the rewards of advertising — whether outspoken or indirect — which they see reaped in abundance by purveyers of cosmetics, tobacco and vapid entertainment, while the doctor remains unpaid and unappreciated. It would seem that the gastro-enterologist is peculiarly susceptible to these evil influences. He should, therefore, struggle with all his strength to maintain the high standards of his specialty, and ever bear in mind the tremendous importance of diagnosis in the carrying out of that particular line of medical practice.

CONCLUSIONS

The specialty of gastro-enterology occupies a wide area in the field of medicine and requires an elaborate background. The proper practice of this specialty demands a peculiarly wide experience in general medicine, a keenly analytical mind, and a willingness to embrace the new, but only when that 'new' gives evidence of correlation with all that has gone before. Many men have been induced to enter gastro-enterology who are fitted neither by training nor inclination for the proper performance of its most exacting requirements. Our calling has been cheapened, and a reproach cast upon all those who have long striven to maintain the standards thus ruthlessly degraded.

The application of the X-ray to gastro-intestinal diagnosis has offered peculiarly easy conditions for inefficiency and fraud to creep in, and for ignorance and egotism to usurp the position which properly belongs to those who have raised the standards now overthrown. It has been demonstrated that gastro-intestinal roentgenography, unallied with roentgenoscopy, and uninterpreted by comparison with the findings of the amemnesis, the physical exploration and the laboratory analysis, is bound to be full of errors.

The confusion of standards existing today in gastro-enterology should be remedied. A legal definition for a gastro-enterologist should be established by suitable medical legislation, as has been done in several other specialties. The man who desires to assume that title should be compelled to submit evidence of his fitness to a competent board. Long practice in general medicine, close association with clinical gastro-enterology in a properly conducted clinic, with post-graduate work supervised by competent authorities — these should be the least of the pre-requisites for registration as a specializing gastro-enterologist. Until such a standard has been legally established confusion will continue to reign, and gastro-intestinal diagnosis will continue to present the contradictions and confusions which it has been the intention of this paper to present for criticism and correction.

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Tumors of the Small Intestine: A Review of the Literature and Report of Eight Additional Cases*

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DURING the past five years there has been an encouraging increase in the number of articles written on the subject of small bowel tumors. Many cases who have died with symptoms of intestinal obstruction have probably had as their etiological factor such undiagnosed tumors. So little is known about tumors of the small bowel and since such few symptoms have their origin within its confines, it may be referred to as "the unknown area" of the abdomen.

The malignant growths occurring in the small bowel are carcinoma and sarcoma. The benign tumors most commonly found are myomas, polyps, hemangiomas, lipomas, adenomas, fibromas and cystic tumors. These benign tumors are usually discovered accidentally at operation or at necropsy for the most part, since probably less than half of them produce any symptoms.

The etiological factors in the causation of tumors of the small bowel are entirely theoretical. The most commonly suggested theories are based upon the absence of abrupt angulations in the small intestine, the fluid nature of its content and the alkalinity of the intestinal fluid. The above listed factors differ considerably from those found in the large bowel. It must be admitted, however, that there is no real basis to account for the rarity of tumors of the small bowel as compared with other parts of the gastro-intestinal tract.

INCIDENCE

At the Mayo Clinic, based upon a study of cases between January 1, 1919, and October 1, 1929, inclusive, carcinoma occurred in the small bowel thirty-one times as compared with 2,775 times in the large bowel and rectum and 2,646 times in the stomach (1). To date Hartman (2) has found only 70 cases of carcinoma and 27 cases of sarcoma of the small bowel at the Mayo Clinic. As compared with the above he found only 44 cases of benign neoplasm. The most common benign neoplasms found were myomas, polyps and hemangiomas. In a review of the statistics of 41,838 necropsies of the Vienna General Hospital, Johnson (3) found 3,585 cases of carcinoma, of which 343 were intestinal; 10 of these were located in the ileum and none in the jejunum. In a series of 780 carcinomata of the intestinal tract, Leichtenstern (4) found only 16 primary in the ileum. Rowley (5) reviewing 15,000 laparotomies at the Hartford Hospital found only one sarcoma and one carcinoid tumor of the small bowel. Gotten (6) of Memphis, was able to find only 4 cases of carcinoma of the small bowel in the records of 20,000 patients at the Polyclinic Hospital. In the same series he found 4 cases of sarcoma, one of which occurred in the ileum of an infant 14 months of age. A study of the records in the Presbyterian Hospital by Parsons (7) revealed 6 cases of small bowel carcinomata, excluding carcinoma of the terminal ileum at or near the ileocecal valve. A series of 82 tumors were reported from the John Hopkins Hospital by Raiford (8) in 1931. The tumors were located between the pylorus and the ileocecal junction and represented 6.5 per cent of all other gastro-intestinal tumors. In this group there were 18 in the duodenum, 14 in the jejunum (7 benign) and 43 in the ileum; location not reported in 7. Forty per cent of the tumors were asymptomatic. Ross (9) reported two cases of intestinal carcinoma in 1931, these being the only cases reported at the Melbourne Hospital between 1922 and 1931, during which time 70,000 out-patients were treated and necropsies performed on 75 per cent of patients dying in the hospital. Hinz (10) found only 18 carcinomas of the small bowel in a series of 584 cases of carcinoma of the intestinal tract. Mueller (11) reported from the Institute of Berlin 5,691 necropsies with 521 cases of carcinoma, 42 intestinal, and of these 42 only 3 were located in the small bowel. Maydl (12) reported 1,460 cases of carcinoma in 20,480 necropsies with 100 cases of intestinal carcinoma, 4 of which were carcinoma of the ileum. Zieman (13) reported 165 cases of carcinoma of the intestine from 21,624 necropsies; 6 were in the ileum. Hellstrom (14), in 1927, collected only 70 cases of carcinoma of the small bowel proven by operation from the literature. He reported 3 cases. In 1929 D'Allaines (15) was able to collect only 114 cases of carcinoma of the small bowel from the literature. Barnhart (16) found only 77 cases of carcinoma of the jejunum and ileum up to the beginning of 1931. From the above data it may be readily seen that the percentage of small bowel carcinomata is much less than the 3 per cent of the intestinal carcinomata which is usually referred to in the literature.

At the Edward Hines, Jr., Hospital from January 1, 1931, to July 1, 1936, a period of five and one-half years, carcinoma occurred in the small bowel six times as compared with 253 times in the large bowel and rectum and 183 times in the stomach. The incidence of carcinoma of the small bowel as compared to the large bowel in this series is 0.027 per cent. During this period of five and one-half years there were 39,444 admissions to the hospital.

SARCOMA

Staemmler (17) found only 33 cases of sarcoma among 54,000 necropsies reviewed. He reports the incidence of sarcoma of the intestines at necropsy as 0.06 per cent and carcinoma of the intestines at necropsy as 1 per cent. He further states that the proportion of sarcoma to carcinoma of the intestines as established at necropsy is about 1 sarcoma to 16 carcinomas, whereas in surgical practice based on statistics by German and Austrian surgeons, it is about 1 sarcoma to 100 carcinomas. Corner and Fairbank (18) collected from the literature 103 cases of sarcoma of the intestines. Sixty-three per cent of this group were located in the small bowel, the largest number being in the ileum and 37 per cent in the large bowel. Nothnagel (19), in 1904, reported 243 cases of intestinal sarcoma out of 24,358 necropsies. Smoler (20) found only

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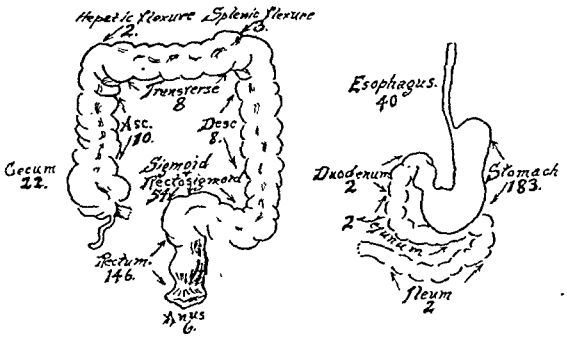


Fig. 1. Carcinoma of the gastro-intestinal tract at Hines Hospital from January 1, 1931, to July 1, 1936.

13 cases of primary sarcoma of the small bowel in 13,036 necropsies at the Prague Pathological Institute between the years 1883 and 1898. None of the cases were in the jejunum and 6 were in the ileum. Speece (21) collected 101 cases of sarcoma and directed attention to the frequency in which they produced intussusception. Sarcoma apparently occurs more frequently in the ileum than in the duodenum or jejunum, the reverse for the incidence of carcinoma. Ullman and Abeshouse (22) collected 125 cases of lymphosarcoma of the small and large bowel and reported 1 case making a total of 375 cases up to 1932. From the study of the 126 cases collected by them, they concluded that lymphosarcoma is twice as common in the small bowel than in the large bowel. The most common location was in the ileum.

In the group of 8 neoplasms reported in this paper taken from 39,444 admissions to the Edward Hines, Jr., Hospital, only one sarcoma was found, its location being in the jejunum.

As has been previously mentioned, Hartman (2) found only 44 cases of benign lesions of the small bowel as compared with 97 malignant neoplasms. In 1928 after making a complete review of the literature, Golden found only 17 reports of cases of non-malignant tumors of the duodenum. In 1924 Brown (24) after making a careful search of the literature found 19 cases of vascular tumors of the intestinal tract below the stomach. In this group were included all forms of vascular tumors, varying from capillary naevi to cavernous angiomas. He reported a case of cavernous hemangioma in the jejunum of a 12-year old girl. In 1917 King (25) was able to find reports of 119 benign tumors of the intestine, only 47 of which were in the small bowel. Only one benign tumor, a hemangioma of the jejunum, has been found at the Edward Hines, Jr., Hospital during the past five and one-half years.

Clifton and Landry (26) reviewed 45 cases of fibroma of the intestines. In 25 of these cases the tumor was located in the small bowel. The tumors were intraluminal in type in all but two cases. Adenomata are generally the most commonly found benign tumors of the small bowel.

AGE AND SEX

Carcinoma: Ewing (27) lists the average age as 46.5 years. The average age for the group of 6 cases of carcinoma of the small bowel reported in this paper was 49.1 years. Rankin and Mayo (1) found the average age of patients with carcinoma in their series of 55 cases to be 47.5 years. Primrose (28) reported a primary carcinoma in the small bowel in an octogenarian. Duncan (29) reported a scirrhous carcinoma in a patient 3.5 years of age. Rankin and Mayo (1) found the ratio with regards to the sexes in their group of 55 cases to be approximately 2 to 1; 37 males and 18 females. Other reports in the literature give a similar ratio.

Sarcoma: In a statistical study of 126 cases by Ullman and Abeshouse (22) the average age incidence was 33.19 years. The ratio for the sexes was 5 to 2, the males showing a greater predisposition for the disease. Corner and Fairbanks (18) found that the age incidence for sarcoma of the small bowel was between 30 and 40 years for the majority of cases. This type of tumor is found most frequently during the first, third and fourth decades. In the series of 59 cases of sarcoma of the small bowel listed by Libman (30) more than 50 per cent occurred between the ages of 20 and 40 years. The youngest patient was five days old.

Benign tumors: In the 35 cases of benign tumors of the small bowel reported by Rankin and Newell (31) the average age of the patient was 38 years, the youngest patient being 14 years of age and the oldest 70. Nineteen patients of the series were males and sixteen females. In the 20 cases collected by Brown (24), vascular tumors of the intestines, both large and small, the age of the patients varied from 2 months to 79 years. In 2 of the cases the age was not stated. The average age in the remaining 18 cases was approximately 41 years. Classification as to sex listed 10 females and 10 males.

SYMPTOMATOLOGY

Carcinoma: There are no characteristic symptoms associated with tumors of the small bowel. The most common symptomatology found in the majority of cases is that of intermittent partial obstruction. Occasionally the first symptoms manifested are the result of an acute obstruction. The usual picture is that of a series of partial obstructions which gradually become more severe. The slowly increasing encroachment of the tumor upon the lumen of the bowel produces the attacks of intestinal obstruction, as stated above, with abdominal pain which may have a paraumbilical or low abdominal location, vomiting, dehydration and finally collapse. The fact that patients may quickly recover from an attack of acute obstruction may be explained upon the basis of food substance which may become lodged temporarily in the constricted lumen of the bowel. As the obstruction increases the proximal bowel becomes dilated, the valvulae conniventes become prominent and the muscle fibers undergo hypertrophy. Fistulous communications may be established between neighboring coils of bowel with the more malignant types of adenocarci-



Fig. 2. Adenocarcinoma of the duodenum (Case No. 1).

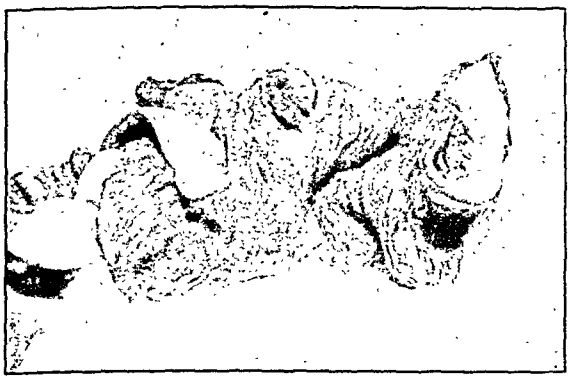


Fig. 3. Tumor of the ileum (Case No. 6).

noma. When the obstruction is situated high in the small bowel and is of the acute type, there is a rapid loss of fluid and solids by constant vomiting and death may occur rapidly from dehydration, demineralization and starvation. The sessile and intraluminal tumors are more likely to produce intussuception.

The most outstanding symptoms of intestinal obstruction are (1) abdominal pain, (2) vomiting and (3) constipation. Abdominal pain is present in practically every case and is the direct result of the vigorous peristalsis initiated to overcome the obstruction. Abdominal distension will be noticed in a large number of cases. Although visible peristalsis is generally mentioned, it is usually a late finding. A history of tarry stools is seldom given. A secondary anemia of varying degrees is usually found. If a mass is palpable, it is often tender and is not fixed in position, but is freely movable.

Sarcoma: The same type of symptoms may be found with the sarcoma group as with the carcinomata. The onset may be gradual and vague or it may begin suddenly as an acute abdominal emergency. Most of the cases of sarcoma reported have a gradual onset since the pathology of the tumors in the majority of cases is of the annular type. The polypoid type growth is more prone to produce intussuception. The alternating constipation and diarrhea found in some of the cases is the result of the stagnation of retained material in the paralyzed and distended loops above the obstruction. When the toxic products cause complete or partial emptying of the distended loop, a diarrhea may result.

Benign tumors: The symptoms of the benign group of tumors is very similar to that of the carcinoma and sarcoma groups. The pedunculated forms are more likely to produce intussuception. These tumors usually occur early in life and may be present for many years before producing symptoms or may not be discovered except during the course of an operation or at necropsy. The symptoms in the cases having encroachment of the tumor on the lumen of the bowel are usually chronic in nature and recur at irregular intervals whereas with the intussuception group the attack will be initiated by a sudden onset of sharp, colicky pain, nausea, vomiting and abdominal distention.

Although roentgenograms are very helpful in determining the presence of intestinal obstruction, the diagnosis is at times very difficult and quite often it is necessary to make examinations at intervals. A flat plate of the abdomen showing distended loops of bowel, especially when intra-intestinal fluid levels are present, is diagnostic of obstruction. In 1928, Case (32) reported that gas and fluid began to accumulate within six to eight hours after obstruction had been established. Roentgenographic examinations may be particularly helpful in ruling out lesions of the stomach, duodenum and colon.

TREATMENT AND PROGNOSIS

Carcinoma: When the tumor is removable, resection should be done restoring the continuity of the bowel with an end-to-end anastomosis. If the tumor is not resectable, a side-tracking procedure must be resorted to.

The prognosis is poor regardless of whether or not the growth is resectable. In the series reported by Rankin and Mayo (1) no patient had at the time of the report lived longer than three years and the average was one year.

The average length of life whether treated surgically or not of the group of six cases reported in this paper was fifteen months from the onset of symptoms. Only one patient lived forty-eight months after the onset of symptoms. Metastasis occurs early in the course of the disease.

Sarcoma: If it is at all possible to cure the patient, a resection of the involved bowel should be done. If the growth is too extensive, a side-tracking operation should be done as a palliative procedure. This may be accomplished by means of an entero-enterostomy, ileocolostomy or colostomy. Both the operable and inoperable cases should receive irradiation since this type of tumor is usually radiosensitive. Although many of the patients die within the first year after operation, there are reports in the literature of patients living more than five years following resection and irradiation.

Benign tumors: More conservative methods are employed in the surgical treatment of the benign group. They may be removed by means of an elliptical incision or by shelling out the lesion from the bowel. If the lesions are extensive, a resection may be done followed by end-to-end anastomosis. In Rankin and Newell's (31) series of 35 patients, all were operated without a single mortality.

Case No. 1. Reg. No. 56310, age 48, white male, was admitted 9-1-34. He stated he was in good health until five months previous to admission at which time he began

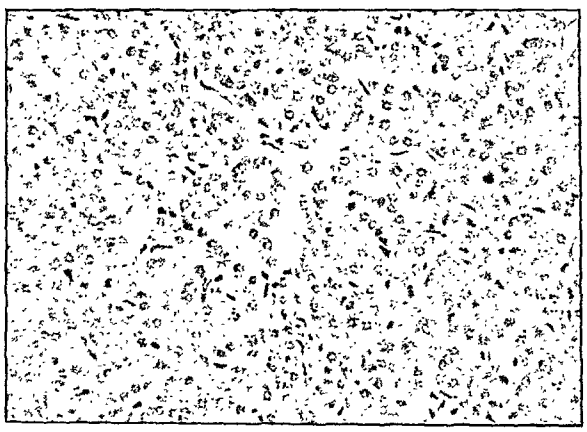


Fig. 4. Adenocarcinoma of the ileum (Case No. 7).

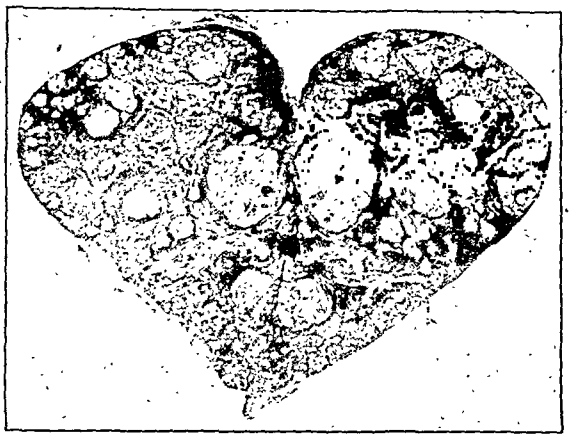


Fig. 5. Metastatic lesions in the liver from an adenocarcinoma of the ileum (Case No. 7).

to notice dull epigastric distress coming on when the stomach was empty and only partially relieved by food and soda. Associated with this was a gradually progressive loss of weight and weakness. Two months prior to admission he consulted a physician who made a diagnosis of duodenal ulcer and patient was placed on Sippy management. This relieved his distress but he continued to lose weight and to become weaker. Three weeks previous to admission he suddenly became icteric. In three days icterus became quite severe. The stools became clay colored and the urine was very dark. There was pronounced itching of the skin. There was no pain, nausea or vomiting associated with this. There was no history of blood in the stools. Weight loss, 55 pounds in five months.

Physical examination revealed a profound icterus of the skin, mucous membranes and sclerae. Patient appeared critically ill. There was tenderness on palpation in the epigastric region. There was a small mass in the right upper quadrant which was movable and smooth and was in all probability the gall bladder. The liver had increased in size.

Laboratory examinations: X-rays—G. I. series were not done because of the critical condition of patient. Erythrocytes 1,600,000, leukocytes 14,600, hemoglobin 40%; polymorphonuclear 92%. After transfusion of 500 c.c. citrated blood, erythrocyte count was 1,960,000; hemoglobin 50%. Urinalysis: albumin, positive, bile positive, many granular casts. Blood chemistry: urea 14.1 mgms., sugar 80. Wassermann and Kahn negative. Icteric index 27. Vandenberg, prompt direct. Feces positive for blood; parasites not found.

Clinical diagnoses: ulcer, peptic, active, severe; carcinoma, pancreas, undetermined; secondary anemia. The patient's condition was such that he did not respond to intravenous medication or blood transfusion sufficiently to enable him to be explored. He expired 9-10-34.

Necropsy revealed (1) ulcer, gastric with secondary hemorrhage; (2) adenocarcinoma of the duodenum, which was considered to have been primary in the duodenum on the basis of malignant regression of a duodenal ulcer, by the pathologist.

Case No. 2. Reg. No. 61759, age 52, colored male, admitted 6-4-35. Patient gave history of a mass starting in the left side of neck of about one year's duration. Patient complained of considerable difficulty in breathing, pain in the chest, difficulty in the passage of bowels, swelling of both legs and ankles, especially the right.

Physical examination revealed a critically ill patient. There was a slight icteric tinge to the sclerae. There was a slight ptosis of the lids. There was a very extensive mass in the left side of the neck which extended from the angle of the jaw filling the entire left side of the neck from the clavicle to the angle of the jaw and extending down on to the chest wall. Several discrete nodules were present on the surface of the mass. There were discrete nodules palpable in both axillae and both inguinal regions. The liver was enlarged on palpation. There was considerable edema of both lower extremities. On rectal examination there were discrete nodules filling the pelvis and the nodules were fixed to the pelvic wall.

Laboratory findings: Urinalysis was essentially negative. Wassermann and Kahn negative. Erythrocytes 4,660,000, leukocytes 7,100; hemoglobin 85%; icteric index 13; Vandenberg, prompt direct. X-ray of neck revealed a new growth, soft tissues of the cervical region. X-ray of chest revealed a heavy shadow of abnormal density which covered the region of the cervical, upper thoracic and left shoulder, giving the impression of an extrinsic lesion. There was no evidence of metastasis within the lung fields. Gastro-intestinal series were not satisfactory on account of the physical condition of the patient. Fluoroscopic examination of large intestine following barium enema revealed considerable deformity in the upper portion of the rectum. The deformity was very irregular and produced considerable constriction. The findings suggested a pathological process, probably a new growth. Definite bony changes were noticed involving the ischia and pubic bones. Histological diagnosis of biopsy removed from node, left axilla, revealed a colloid carcinoma.

Patient was given deep X-ray therapy to the mass in the neck producing very little change in its size. The patient died 7-18-35.

Necropsy revealed carcinoma of the duodenum with extension to adjacent structures and metastases to the liver, suprarenal glands and skeletal system.

Case No. 3. Reg. No. 44331, age 48, white male, admitted to the hospital 9-29-32. History dated back to the first week in May, 1932, at which time he suddenly developed an acute generalized abdominal pain two hours after eating. The pain was quite severe. The patient did not vomit or have any other gastro-intestinal symptoms. The pain continued fairly constant for about four days and then gradually disappeared. A local physician was consulted, but no diagnosis was made. The patient lost from ten to twenty pounds in weight in about two months. The pain suddenly recurred about July 15. The pain was similar in type to that of the original onset, but was not as severe. Since July, 1932, he had felt a tender mass situated near the umbilicus. There was no history of passage of blood per rectum.

Physical examination revealed evidence of considerable loss of weight. There was no cervical, supraclavicular or axillary adenopathy. There was an enlarged firm node in the right inguinal region. There were no definite abdominal masses palpable. Rectal examination revealed a very large firm, nodular mass which apparently had not originated in the rectum.

Laboratory findings: Urinalysis negative. Wassermann and Kahn negative. Blood count: erythrocytes 4,360,000; leukocytes 9800; hemoglobin 80%. Guinea pig inoculations of specimens from right and left ureters revealed no evidence of tubercle bacilli on necropsy. X-ray findings, gastro-intestinal tract, revealed no demonstrable evidence of the gastro-intestinal tract or gall bladder. X-ray of chest was negative. X-ray of genito-urinary tract was normal. Histological report of biopsy removed from right inguinal region revealed a metastatic adenocarcinoma.

Deep X-ray therapy to abdomen and right inguinal region was given affording the patient some relief from his pain and patient was discharged upon his own request 12-13-32 with a diagnosis of adenocarcinoma, metastatic, primary source not known. Patient had a recurrence of his symptoms and was admitted to another hospital where he expired on 2-16-33. Necropsy revealed a primary carcinoma of the jejunum with extension to the peritoneum

and regional lymph nodes and metastases to duodenum, liver, spleen and pancreas.

Case No. 4. Reg. No. 53060, age 43, male, white, admitted to the hospital 3-24-34. Patient stated that he noticed a small lump just above the umbilicus for the past 6 years. Also about the time he noticed this mass he began having cramping pains in his abdomen which occurred at irregular intervals. His appetite became impaired and he had frequent attacks of vomiting which would partially relieve the abdominal pain. He lost about 40 pounds in weight during the period two to three years prior to admission. The abdominal mass gradually increased in size. Five months previous to admission he was operated upon at a private hospital. At operation a mass involving the small bowel about eighteen inches from the pyloric end of the stomach was found. This mass was removed and an anastomosis of the small gut made, drainage introduced and the abdomen closed. Biopsy report from the National Pathological Laboratory, St. Louis, Missouri, was carcinoma of the small bowel (jejunum). Since operation patient had abdominal pain and nausea at frequent intervals. There was no history of passage of blood in the stool.

Physical examination revealed a fairly well nourished and developed white male, appearing chronically ill. There was a post-operative hernia present in his operative scar. There was a mass palpable to the left of the abdomen.

Laboratory findings: Urinalysis was essentially negative. Wassermann and Kahn negative. Blood count 4,500,000 erythrocytes; 10,000 leukocytes, 85% hemoglobin. X-ray examination, gastro-intestinal series revealed a normal gall bladder and normal stomach. Barium enema revealed a normal colon.

Because of recurrence of patient's symptoms and because of the palpable abdominal tumor, the patient was explored. A large intraabdominal tumor (retroperitoneal) was found. There were numerous adhesions between the liver and abdominal wall and between the omentum and abdominal wall and between coils of small intestine, producing partial obstruction. An anastomosis was made between a distended loop and a collapsed loop of small bowel. Patient did not react favorably following operation and died 8-15-34, approximately three months following the operation.

Necropsy revealed an adenocarcinoma of the jejunum with ulceration and perforation and regional metastases.

Case No. 5. Reg. No. 62391, age 43, white male, admitted 7-3-35. Patient gave a history of having had a moderate distention of his entire upper abdomen associated with a cramplike pain and marked tenderness of abdomen upon palpation. Onset was about six months prior to admission during which time he lost about 25 pounds in weight. There had been no nausea, no vomiting and no passage of blood per rectum.

Physical examination revealed a chronically ill patient in poor condition. Two large abdominal scars were noted which were the results of previous appendectomy and cholecystectomy done elsewhere. Abdomen was distended and patient complained of marked tenderness on palpation, making the examination unsatisfactory. However, no masses could be definitely palpated. Liver was not enlarged. There was an enlargement of the lymph nodes in the right axilla.

Laboratory findings: Urinalysis essentially negative. Wassermann and Kahn negative. Erythrocytes 4,150,000; leukocytes 13,000; polymorphonuclears 84%; hemoglobin 70%. Examination of sputum revealed no tubercle bacilli. Histological report of biopsy removed from right axillar revealed tuberculosis. Fluoroscopic examination of large intestine following barium enema revealed a normal colon. Examination of chest by X-ray revealed no evidence of metastasis.

Patient developed pneumonia while in the hospital and expired 9-10-35. Necropsy revealed a lymphosarcoma, primary in the jejunum with involvement of adjacent lymph nodes.

Case No. 6. Reg. No. 52769, age 62, white male, admitted 3-9-34. Patient stated that about five months previous to admission he began to have frequent pains, particularly in the lower half of abdomen. There was no history of vomiting or icterus. Patient had lost about 68 pounds in weight over a period of five months. There was no history of passing of blood per rectum. Prior to admission to hospital patient developed severe diarrhea.

Physical examination revealed a markedly emaciated senile white male, who appeared seriously ill. The liver was enlarged about two fingerbreadths below the costal margin. Patient complained of tenderness in the right upper quadrant on deep palpation. There was also a palpable mass in the right upper quadrant which was probably the result of metastasis to the liver.

Laboratory findings: Wassermann and Kahn negative. Urinalysis, albumin positive; coarsely granular casts present. Blood count: erythrocytes 4,200,000; leukocytes 23,000; polymorphonuclears 75%; hemoglobin 80%. Gastro-intestinal series revealed a pathological process situated near the pyloric end of the stomach. Upon fluoroscopic examination of the large intestine the examiner was unable to rule out a new growth.

Clinical diagnosis: Carcinoma, metastatic to liver, primary site unknown, inoperable. Shortly before patient's death he developed pneumonia and expired 5-15-34. Necropsy revealed an adenocarcinoma of the ileum with metastases to liver and regional lymph nodes and bronchopneumonia.

Case No. 7. Reg. No. 34699, age 42, white male, admitted to the hospital 7-23-31. He was admitted in a critically ill condition for treatment of gastric ulcer. He gave a history of having had a gastric ulcer for several years. He was previously hospitalized for three to four months for treatment of this condition at another hospital. On this examination he complained of severe cramping pain epigastric region of several days' duration. He stated he was quite restless and had vomited greenish material at frequent intervals. Pain was quite severe.

Physical examination revealed a critically ill patient who gave evidence of having lost considerable weight. There was vigorous active peristalsis present. Signs of intestinal obstruction were quite evident.

Laboratory findings: Urinalysis essentially negative. Wassermann and Kahn negative. Blood count: Erythrocytes 4,800,000; leukocytes 8,600; polymorphonuclears 64%.

Patient was explored several hours following admission. At the time of operation there was considerable bloody



Fig. 6. Hemangioma of the jejunum (Case No. 8).

fluid in the abdominal cavity. There was a spontaneous rupture of the ileum near its terminal portion. A mass was found in this same region. Because of the condition of the patient an enterostomy was done and the abdomen closed as rapidly as possible. Patient developed an acute generalized peritonitis, which had apparently formed before operation, and he died 7-28-31.

Necropsy revealed an adenocarcinoma of the ileum with perforation and metastasis to the liver and purulent peritonitis; surgical enterostomy in the jejunum.

Case No. 8. Reg. No. 51987, age 46, white male, admitted 1-30-34. Patient stated he was apparently in good health until six weeks previous to admission at which time he developed a pain in the upper part of his chest. The pain later left the chest region and settled in the epigastric region. Pain was dull in nature and constantly present. Food seemed to relieve the pain at times. He lost twenty pounds in weight during the previous fifteen days to admission as a result of the severe vomiting spells which he had during this time. There was no history of constipation or passage of blood per rectum.

Examination revealed an enlarged liver two fingerbreadths below the costal margin. There was a palpable mass in the right hypochondrium. Patient also complained of tenderness upon deep palpation over this region.

Laboratory findings: Urinalysis essentially negative. Wassermann and Kahn negative. Blood count: 4,600,000 erythrocytes; 15,200 leukocytes; 72% polymorphonuclears; 85% hemoglobin. Blood chemistry: N.P.N. 36.4 mgm. Feces positive for blood. Fractional gastric analysis normal. Flat plate of abdomen normal. X-rays of gastrointestinal tract apparently normal; gall bladder normal. X-ray of chest normal.

Patient was explored on 3-9-34. A small tumor was found in the jejunum about 10 cm. from the Ligament of Treitz. The small tumor was excised and the incision through the intestine closed in two layers, using fine chromic catgut and silk. Histological examination of section of small intestine removed revealed a cavernous hemangioma. The tumor was composed of blood vessels and channels having as their basic factor a stroma consisting of loose connective tissue. Patient was discharged symptom free.

CONCLUSIONS

1. The incidence of carcinoma of the small bowel is less than one-half of one per cent in this series.
2. Sarcoma is more frequently found in the small bowel than in the large bowel.
3. Sarcoma apparently occurs more often in the ileum than in the duodenum or jejunum, the reverse being true for the incidence of carcinoma.
4. There are no characteristic symptoms associated with tumors of the small bowel. The most common symptomatology found in the majority of cases is that of intermittent partial obstruction.
5. The majority of cases of benign tumor and of sarcoma occur between the ages 30 to 40 whereas carcinomata are more often found in patients from 40 to 60 years of age.
6. A flat plate of the abdomen showing distended loops of the bowel, especially when intra-intestinal fluid levels are present, is diagnostic of obstruction.
7. Roentgenographic examinations may be particularly helpful in ruling out lesions of the stomach, duodenum and colon.
8. The treatment of a malignant tumor should be by resection, if the tumor is operable, restoring the continuity of the bowel by end-to-end anastomosis. If inoperable, a side-tracking procedure must be resorted to. Post-operative irradiation should be given to sarcoma cases whether operable or inoperable.
9. The prognosis is poor for malignant tumors whether operable or inoperable.
10. Metastasis occurs early in the disease and involves adjacent structures first.
11. More conservative surgery should be employed in the treatment of benign tumors of the small bowel.
12. The prognosis is excellent for the benign tumor cases.

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The Mechanism of Milk Clotting*

II. Role of Hydrogen Ion Concentration

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THE course of clotting has been followed varying the pH of milk and the phenomena observed throughout the physiologic range of pH. The experiments were carried out at 37° C. in a thermostat and the pH measurements made with a quinhydrone electrode except in cases where the pH was varied with standard buffer solutions. The role of the individual components have been previously evaluated in the clotting process (1).

(1) Changes in the Hydrogen Ion Concentration During Clotting.

The pH of each of the clotting components was measured as a basis for comparison with the final pH

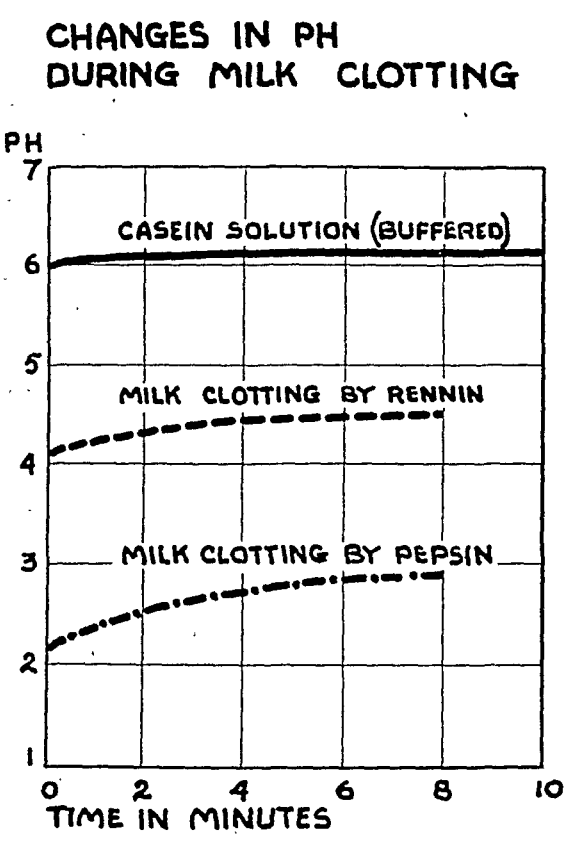


Fig. 1

of the mixture and the pH changes effected during clotting. Once the initial equilibrium cH values was established the changes in cH were followed potentiometrically at definite time intervals. An initial short range clotting period of the buffered synthetic clotting system showed no change in pH during coagulation. On measuring the cH during the clotting of the casein system without added buffer solution, the variation in cH was slight and indefinite. A cH study during the rennet clotting of milk also showed no change in cH

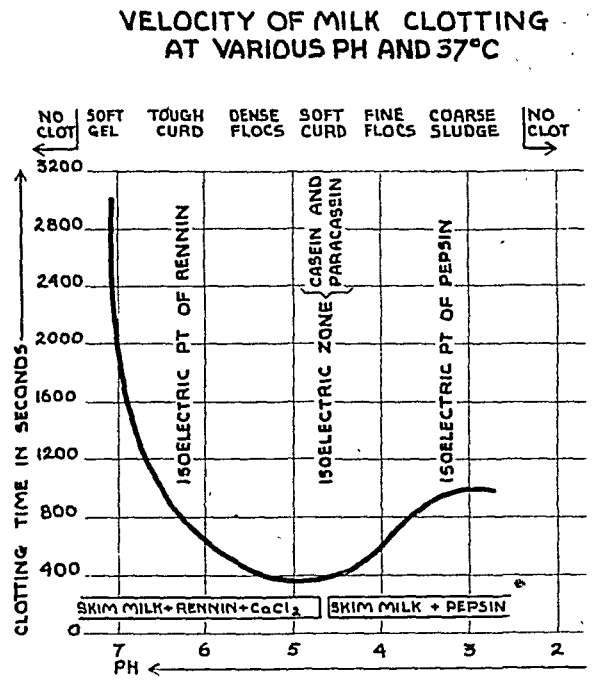


Fig. 2

at about pH 6.0 within the range of maximum rennet activity. But on studying similar solutions at more acid pH using pepsin, a small but definite diminution in cH maintained (Table I). Apparently the high buffer action of milk at about pH 6.0 obscures any change in cH during rennin clotting. But the low buffer value of milk at pH 2.0 does not interfere with the small cH change during pepsin clotting. The change in cH during clotting represents a continuous phenomenon (Fig. 1). The rate of diminution of hydrogen ions is great at the first intervals but gradually falls off an asymptotic limit. The paracasein formed adsorbs H in the process at least by pepsin clotting.

(2) Limits and Optimum of pH for Milk Clotting.

That alkalies prevent the clotting of milk is generally known. But the rate of clotting, the degree of clot formation and the character of the clot are greatly affected by pH. These factors are particularly

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significant for gastric digestion. Since milk may be precipitated by proteolytic enzyme or by an acid, both types of coagulation were studied. The pH of synthetic clotting solutions was maintained by standard buffer solutions, the pH of milk adjusted with HCl or NaOH and controlled potentiometrically.

Milk coagulates spontaneously at various pH zones of acidity. They pertain to skimmed or whole milk

TABLE I

pH change during clotting

Time (min.)	Casein Solution	Milk — Rennin	Milk — Pepsin
0	6.0	4.1	2.2
2	6.0	4.2	2.5
4	6.1	4.4	2.6
6	6.1	4.5	2.7
8	6.1	4.6	2.8
10	6.1	4.6	2.8

although the pH values are clearer for fat-free milk. Casein precipitates at its isoelectric point about pH 4.7 from both milk and casein solutions. On the acid side of this pH casein forms insoluble casein salts, the maximum precipitation appearing between 2 and 3 (Table 2). On the alkaline side of the isoelectric point casein forms relatively soluble metal caseinates. In the phosphate buffer solution no coagulation appears unless $CaCl_2$ is added to form calcium caseinate insoluble until about pH 6.5. Its solubility however, increases progressively with increasing pH. Addition of Ca++ is unnecessary below pH 4.7 because no calcium caseinate is possible since casein chlorides and the like are formed. The coagulation of a synthetic system at various pH media was observed at 37° C. The pH zone of coagulation was rather limited between 6.0 and 6.5, fine opalescence appearing above pH 6.5 and coarse turbidity below pH 6.0.

The rennet coagulation of skimmed milk showed a much wider pH range for clotting (Table 4). On the alkaline side of pH no clot formed. Paracasein has its charge increased and stabilized by OH as well as by other anions Cl, CO_3, HPO_4, $C_6H_5O_7$, citrates, etc. It is not due to precipitation of Ca++. Clotting was greatly prolonged near pH 7.0 but as the cH increased

TABLE II

Spontaneous coagulation of milk

pH Range	Buffer Solutions	Coagulation pH Milk	Coagulation pH Casein
1 —	Glycocoll — HCl	2.8	2.5
3.5 — 5.5	Acetate — Acetic	4.8	4.7
5.5 — 8.0	Phosphates	ppt. to 6.5 (added $CaCl_2$)	—

the duration of clotting rapidly diminished. The optimum zone is about pH 6.0 which coincides with the range for complete conversion of casein to paracasein. The clot assumed the form of a gel soft in consistency near pH 7.0 and firmer with increasing cH until about pH 5.0 when the coagulation became coarse, apparently the result of acid precipitation.

Since the maximum activity of rennin is about pH 6.0 it is not surprising that the acid nature of the coagulation becomes manifest at about pH 5.3 and failure of clot formation beyond pH 7.0 where rennin

TABLE III

pH and Rennet coagulation

5% Calcium Caseinate 25 c.c. 1% Rennin Solution 0.2 c.c. 0.2 N $CaCl_2$ 5 c.c.	
pH (Buffered)	Clot Time
5.8	turbidity
6.0	8′
6.2	7′
6.4	10′
6.6	16′
6.8	opalescence

is destroyed and calcium paracaseinate is soluble. The region between pH 6.0 and pH 5.0 is transitional for both rennin and acid precipitation respectively. The zone of rennin action is not an extension of the acid precipitation. Indeed the precipitation zone with rennin is much broader than with acid alone. Rennet makes the possibility of precipitation much more certain than with the narrow optimum for acid precipitation. The rennet precipitation optimum of paracasein is near pH 6.2 while the acid precipitation optimum is near pH 4.7. The rennet clotting optimum

TABLE IV

pH and milk clotting

Clotting System at 37° C. Skim Milk 25 c.c.			
1% Rennin 0.2 c.c. 0.2 N $CaCl_2$ 5. c.c.		Pepsin 1 c.c.	
pH	Clot Time	pH	Clot Time
5.0	300 sec.	2.0	
5.3	400	2.2	1000 sec.
5.7	420	2.5	950
6.0	460	2.7	900
6.2	600	3.0	850
6.4	850	3.2	810
6.6	1050	3.5	800
6.8	1300	3.7	700
7.0	1800	4.0	600
7.5		4.2	450
		4.5	400
		4.7	370

at about pH 6.2 yields practically 100% of clot while near the acid clotting optimum the rennet clot yield is nil. At about pH 5.0 half of milk is clotted with rennin.

Syneresis or clot retraction occurs with the rennin

clotted milk between pH 7.0 and 5.0. It becomes more marked toward the isoelectric point of casein for in more acid media the clot is less stable in dispersion. The greater attraction between the coalesced particles squeezes out the liquid between them, the rate of such contraction increasing with the concentration. The properties of milk curd will be considered in a forthcoming study.

The coagulation of skimmed milk below pH 5.0 was determined with pepsin (Table 4). The clotting time assumes a minimum at about pH 4.8 but increases with rise in pH. The clotting duration appears greatest at about pH 2.7. With increased cH however the rate of coagulation becomes increasingly faster. On the acid side of the isoelectric point of casein the clot was granular and no syneresis was observed. While clotting time diminishes at pH values below the broad maximum 2.5-3.0, clotting is inhibited below pH 2.0 (Fig. 2). Clotting time studies at higher temperatures indicate steeper gradients broadening at lower temperatures.

SUMMARY

Rennet clotting of milk is accompanied by no change in the hydrogen ion concentration but pepsin clotting shows an asymptotic diminution in the hydrogen ions due to their adsorption by paracasein. Milk coagulates spontaneously at various pH zones, insoluble casein salts being formed between pH 2.0 and 3.0, isoelectric casein at pH 4.7 and calcium caseinate at about pH 6.5. Optimum rennet coagulation is at about pH 6.0 coinciding with complete conversion of casein to paracasein. At about pH 5.3 acid precipitation is initiated and rennin activity practically ceases. The rennet zone is broad and the acid zone narrow; the optimum of the former is pH 6.2 and that of the latter is at pH 4.7. The rate of clotting with pepsin diminishes in more acid ranges until 2.7 when it increases again. At alkaline pH no clotting takes place.

The role of the hydrogen ion concentration in milk clotting has been considered more from the standpoint of digestion and absorption of milk from the alimentary tract rather than from its function in the actual mechanism of milk clotting (2). In this respect both hydrogen ion concentration and pH range affect the clotting of milk as they do the clotting of blood (3).

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Editorial

SIDELIGHTS ON PROCTOLOGY*

AN examination of the written records of the past tends to induce a healthy attitude of humility in a medical man of any field. It is immediately found that fundamental medical methods and surgical procedures do not germinate spontaneously but are slowly evolved with the turn of the centuries, and that in the words of the prophet "All knowledge is but a remembrance and all discovery but a forgetting." Nowhere is this more evident than in proctology, where a lively interest existed on the part of the most ancient practitioners. Hundreds of years before Christ, the Egyptians recorded their findings in proctologic examinations; Hippocrates, born on the Island of Cos in 460 BC, left descriptions of fistulas and hemorrhoids and instructions concerning their treatment which would not be out of place in a text book of today; Aurelius Cornelius Celsus writing his "De Medicina" during the region of "Tiberius," included accurate descriptions of colitis and the dysentaries and recommended the use of the scalpel in the cure of fistula.

Records of this sort also induce a glow of pride in our historical heritage. In recent years through an orderly and wise process of evolution, proctology has identified itself as a subdivision of surgery and we have therefore come to have an impelling interest also in the story of surgery whose struggle for a place in the medical sun during the seventeenth and eighteenth centuries offers a rather curious counterpart of the travail through which our specialty has passed more recently.

In the 17th century the surgeon was still bound to the barber in a union which has become distressing, the United Company of Barber-Surgeons which had been chartered by Henry the 8th a century before, was not to be dissolved into its component groups until the 18th century. Denied the use of the title of Doctor by his medical confreres of the long gown, he was during this period of a tribe against whom every man's hand was turned.

In England, it was a Cavalier, a loyal follower of Bonnie Prince Charlie in his exile and "Surgeon in Ordinary to His Person" when he became Charles II, who was to lead the English surgeon into the promised land. This Richard Wiseman, like his great contemporary in the medical field, Sydenham, was primarily a soldier, like Sydenham he was a forerunner of modern methods and manners of thought. After completing his seven years of apprenticeship, he had served in the armies of Holland, of Spain, of Charles the 1st of England and later in those of his son. With the Restoration of the Monarchy, he became the first consulting surgeon of his time and at the age of 43, Master of the Company of Barber-Surgeons. His Surgical Treatises, which described his experiences in the diagnosis and treatment of a wide range of lesions including diseases of the anus, demonstrated that he was a man far ahead of his time and in England elevated surgeons from the tonsorial status to that of a respected profession. In France, the surgeon was in even greater disrepute, the itinerant and quack being often more highly respected. Late in the 17th century however an event occurred which has been said to have been more important to the prestige and consequent advance of surgery than all the teaching of the French master surgeon, Pare'. On November 18th,

*Address delivered at the Annual Dinner of the American Proctologic Society, Atlantic City, June 8, 1937.

1687, Louis 14th, the Sun King, was operated upon by his Surgeon in Chief Monsieur Felix de Tassy.

The royal patient had been afflicted with fistula for a year, during which courtiers and quacks extolled various remedies. The King sponsored a massive experiment, in which the most promising of these infallible remedies were applied to various of his subjects similarly afflicted. No one was cured after a year's trial and consequently permission was granted to the surgeon to incise the royal flesh. A curved and guarded scalpel was used, now known as the royal bistory; the operation resulted in a complete cure; the surgeon, his eight assistants and the boy who carried the hot water received altogether a fee of $73,000, a standard not exceeded until Mr. Lockhart-Mummery journeyed to far-off India to cure a Maharajah. The complaint became extremely fashionable in the Court and throughout France. It is said that Louis the 14th influenced medicine in three curious ways, his attack of typhoid fever gave immense vogue to the use of antimony, his anal fistula brought about the rehabilitation of French surgery, and the fact that his mistress was attended by Clement the royal accoucheur did much to further the cause of male midwifery.

From these beginnings has the art and science of surgery reached its present eminence and as surgeons we exult in its continued progress.

Proctology as a specialty was a product of the nineteenth century and it is good to feel that our craft is actuated by the same idealism and scientific honesty which motivates our confreres in the wider field. The constant flux in proctologic opinion, with increasing clarity of insight is apparent to one who peruses the pages of medical literature covering the diseases of the ano-rectum. It may interest you as it did me, to take a short journey, by way of contrast, through the Transactions of this Society and contemporaneous literature of 1913, a year I have selected because it marked my own passage through the first portals of medical study.

Dr. Joseph Matthews, the first physician in the world to limit his work to this field, was for the second time President of this body, succeeding Dr. Louis J. Hirschman. The problem of the proper bounds of the specialty was one of evident concern and the opinion was offered from the floor of this Society that while urologic and gynecologic lesions could well be disregarded by the proctologist, the structural uniformity of the intestinal tract, its exposure to the same agents of disease and the interdependence of all intestinal diseases rendered as logical the inclusion of the entire tract.

Dr. Jerome Lynch proposed a plan for blocking the abdominal sympathetic nerves which foreshadowed the work of Finsterer and Kappis; Dr. Dwight Murray offered a fourth report on the subject of pruritus ani, based on an enthusiastic belief in the relief to be obtained from the use of his streptococcic vaccine, while Dr. Hanes, acid and castor oil undiscovered, advocated surgical drainage and cauterization. Fistula enjoyed the same diversity of treatment afforded four hundred years before Christ when Hippocrates discussed the comparative merits of the scalpel, the ascharotic and the seton. Dr. Robins of Virginia and Dr. Riggs of South Dakota, called attention to the facility with which a flap of rectal mucosa could be slid down to cover the internal opening and suggest that all fistulae arise from thrombotic internal hemorrhoids. Mr. Mummery advocated incision but not excision of the fistulous tract.

Dr. Harvey Stone of Baltimore, entered a spirited defense of the Whitehead operation, although his records indicated that 37 out of 185 cases complained of "weakness of control of the bowel." Another author advocated electrolysis as a painless, safe method of treating all cases of internal hemorrhoids.

Several cases of rupture of the intestine from introduction of the new sigmoidoscope were reported and it was suggested that introduction under anesthesia presented perils as did the use of too vigorous inflation, made unnecessary by use of the position Dr. Hanes had suggested.

Amebic dysentery was a fruitful subject for discussion, as the exponents of appendicostomy or cecostomy (Dr. Jelks, Dr. Beach, Dr. Gant), were now hearing of the new specific, emetin, just discovered by Major Leonard Rogers of Calcutta, which had been found to have marvelous effect in the type of dysentery in which the parasites were demonstrated but not in the "bacillary" type.

The "Irritable Colon" of 1937 presented the same complexity of syndrome and multiplicity of treatment a quarter of a century ago under the names "myasthenia gastro-intestinalis," "membranous enteritis" and "colica mucosa."

Pilo-nidal sinus was discussed as an interesting anomaly by Dr. Krouse, who disagreed with the current opinion that the presence of hair was due to broken hair from the exterior being pushed into the sinus through its entire length and stitched the lining membrane to the skin, in another the tract was laid open and curetted, in a third the tract was excised on a probe and the parts approximated.

Dr. Dan Jones was already sounding the warning that rectal cancers came to surgery too late, and Dr. Jelks still hale and hearty in 1937, in 1913 gave a vigorous exhortation under the title "Crude and Careless Diagnostic Methods" which ended more or less as follows":

And now that life's end is near approached, our retrospection brings to mind the following verses:

> "Life is an experiment, whose proof is real
> That which you think, you live and feel;
> Think, feel, reap and learn to grow,
> For life is worth just how much you know."

The Oath of Hippocrates prescribes that the pupil shall cherish and support the Master who taught him the Art and regard as brothers the sons of his preceptor. In the confines of this small group are gathered all my preceptors as well as former fellow neophites in the art and science of our specialty and I should be ungrateful indeed if I failed to feel for this association an enduring affection as well as an honest admiration because of its thirty-eight years of service to the medical profession and to humanity.

These annual gatherings are to me refreshing opportunities for scientific rehabilitation and pleasant fellowship, the Society is to be especially congratulated upon the unusually large group of wives and daughters who grace the occasion. To these charming women who share so bravely our sorrows and rejoice

with us so sincerely in our successes I offer a toast in the words of Tagore:

O Woman, you are not merely the handiwork of God, but also of men; these are ever endowing you with beauty from their hearts.

Poets are weaving for you a web with threads of golden imagery; painters are giving you form over new immortality.

The sea gives its pearls, the mines their gold, the summer gardens their flowers to deck you, to cover you, to make you more precious.

The desire of men's hearts has shed its glory over your youth. You are one-half woman and one-half dream.

Curtice Rosser, Dallas, Texas.

ERRATUM

In the article "An Office Procedure for the Rapid Estimation of Pepsin and its Clinical Significance," by Drs. Barowsky, Tauber and Kleiner, appearing in the June issue, note the following correction. In all four tables under the headings "FREE HCl" the words "c.c. N/100 per c.c." should have read "c.c. N/10 per 100 c.c."

Book Reviews

Synopsis of Digestive Diseases. By John L. Kantor, Ph.D., M.D., 286 pages; C. V. Mosby Co., St. Louis, Mo.

THIS is a concise yet comprehensive and very informative review of the diseases of the digestive system.

The first part of the book is devoted to such important general considerations as classification of digestive disorders, diagnostic and therapeutic methods, and organic and functional inferiorities including the neuroses.

There then follows a more detailed consideration of the diseases affecting the various parts of the gastro-intestinal tract and its accessories such as the liver, gall bladder and pancreas. This section includes an adequate though not lengthy discussion of the etiology, pathology, symptoms, diagnosis, prognosis and treatment of the various organic disturbances of the digestive system.

The last few chapters are concerned with intestinal parasitic infestation and provide a very helpful review of the life history, mode of spread and the other general considerations of various intestinal parasites and the pathological changes they produce.

In the closing chapters there is a brief discussion of the more important extra-digestive diseases with digestive manifestations.

This small, well-bound book, although a synopsis of digestive diseases, is indeed a comprehensive review and should be welcomed by the general practitioner and the gastro-enterologist.

Hanes M. Fowler, Fort Wayne.

Take Care of Yourself. By J. W. Ephraim. New York, Simon and Schuster, Inc., 1937.

HERE is another book for the guidance of the unwary purchaser of cosmetics and the type of drug that is commonly found in the family medicine cabinet. Fortunately Mr. Ephraim spends little time in harrowing his readers' feelings and trying to scare them and horrify them over the dangers to life that lurk in many a proprietary drug or food. He spends most of his space on positive advice about the buying of drugs and cosmetics and about the care of the teeth, skin, hair, feet and bowels. There are chapters about shaving, sunburn, colds, indigestion, weight reduction, vitamins, antiseptics, "pain killers," sleep and "hangovers."

There is much good advice, and for a layman, Mr. Ephraim has done very well. The specialist can cavil here and there, and perhaps he will not be as optimistic about curing things as Mr. Ephraim is, but on the whole he will say the book is useful and helpful.

Ephraim is on surest ground in the last chapter in which he points out to consumers that they have themselves to thank for the fact that daily they are robbed and gypped and flimflammed. If they weren't so credulous and so easily influenced by false advertising it wouldn't pay the manufacturer to spend millions on attractive copy. When once the writer of this review suggested to an intelligent college graduate that instead of buying Countess de Pom Pom's rejuvenating facial food for five dollars a small artistic jar she buy exactly the same cream from Ephraim for 50 cents a large jar, she answered that although she didn't have much faith in the Countess and was willing to admit that she was being gypped, the expensive stuff gave her a certain feeling of satisfaction and hopefulness that the other did not, and so she would go on buying the fancy little jar — which shows again that human nature demands deception and that people will always pay well anyone who will cater to their wishful thinking.

W. C. Alvarez, Rochester, Minn.

Annual Abstracts of Proctologic Literature 1935-1937

By CHARLES E. POPE, M.D., Evanston, Illinois

LYMPHOGRANULOMA INGUINALE

Grossman reports 5 cases and Bacon in the same report discusses 94 cases studied at the Graduate Hospital in Philadelphia the past 4 to 5 years, stating that 46% showed positive Wassermans and 40 cases were treated with fuadin and tartar emetic but with discouraging results.

Hayes et al discusses the subject in complete and excellent fashion. Striking results were obtained in the inguinal adenitis cases, 14 cases becoming well with intravenous Frei antigen and marked general improvement occurring in other cases such as the fistulas and strictures.

From experimental observations *Hellerström* reports lymphogranuloma inguinale is an infectious disease due to probably an invisible unfilterable virus, 100% transmissible to apes and white mice but questionably to guinea pigs, is slightly glycerine resistant, stands cold temperatures, is lymphotrophic in nature, produces antibodies of virulicidal character, and may be demonstrated in the regional lymph glands in men shortly after infection. Animal inoculation has shown esthiomene to be etiologically synonymous with lymphogranuloma inguinale. The antigen used intravenously in 13 cases has proven of diagnostic value and therapeutic and theoretic interest.

Kondo reports a case of peritonitis with bloody serous fluid with retroperitoneal and mesenteric lymph node involvement in which the abdominal fluid injected into apes intracerebrally transmitted the disease and gave a positive Frei reaction. No bowel pathology accompanies. Meteorism, perirenal inflammatory reaction, a hematoma formation and a retroperitoneal phlegmon accompanied thought due to the above reason to the virus of lymphogranuloma inguinale.

C. Martin and *Bacon* review all phases of this disease in one of the most outstanding papers written. The article is practically a monograph and contains 371 references. They report the varied findings in 136 cases. They state "the disease is of interest by virtue of the fact that we realize that it is not new, that many cases of inguinal buboes have been and are manifestations of this disease, that inflammatory rectal strictures, which occur particularly in women are most frequently the result of a perirectal lymphongitis initiated by the specific virus of lymphopathia venerea, and that esthiomene and chronic elephantiasis or the combination of these as the genito-anorectal syndrome or the anorectal siphiloma are part of the same affection. Of considerable interest is the marked improvement of one case with inguinal adenitis to intravenous injection of the Frei antigen.

Purcell and *Finlaysen* report a rare case of lymphogranuloma inguinale following an intraurethral lesion.

Rainey and *Cole* report 41 cases of lymphogranuloma inguinale giving detailed findings in 23 cases. The Frei test was positive in all cases where inguinal adenitis, ulcerative proctitis, and rectal stricture were associated findings, but was negative in all of the control cases used. A positive Kahn in 28.5% was considered merely coincidental. 87% were negroes.

Vander Veer, Cormia and *Ullery* report 47 cases, 26 of which showed inguinal adenopathy and a positive Frei test and 21 cases which showed

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rectal stricture in which class 70% showed a positive Frei. 85% were colored patients.

Von Haam and *Lichtenstein* in a review and analysis of the case histories in the Charity Hospital believe that 20% of the 1285 rectal strictures present from 1911 to 1933 probably were lymphogranuloma cases. Seven local strains of the causation organism were isolated from inguinal buboes and successfully transmitted to experimental animals in a study of 154 definitely diagnosed cases. 86 were males and 68 females. 13% were white in the male group whereas only one white female was present. The age incidence was greatest between 20 and 30.

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PILONIDAL CYSTS AND SINUSES

Breidenbach and *Wilson* review 288 cases from the surgical services of the Bellevue Hospital, N. Y. C., and favor complete excision. A follow up of 83 cases showed this method gave 94% cures. The authors believe this condition is one of a congenital faulty skin development.

Rogers and *Hall* review 181 cases of pilonidal sinus at the Massachusetts General Hospital. Where radical excision was done and partial or complete closure attempted poor results were experienced due chiefly to infection rather than retained tissue. Dye when used usually hindered the excision due to its not penetrating the sinus fully and staining normal tissue. The authors report a new method which permits ambulatory management. A mid-line post-sacral incision is made and a lateral under-cutting excision on either side is made of the sinus tract and tissue. The wound is packed with antiseptic soaked gauze and the wound is recauterized and dressed postoperatively from time to time. Healing occurred in 6 weeks. No extension occurred below the coccygeal fascia in any of their cases.

Gage reports a case showing embryonic neuroglia cells and fibrils extending into the sacral canal and therefore believes that the classification should include this type as well as the usual type with extension down to or near the periosteum of the sacrum. Demonstrates the sacrococcygeal dimple as being a caudal ligament attachment to the skin in agreement with Oehlecker, Ravdin and Johnston.

Ravdin and *Johnston* report a series of cases at the Hospital of the University of Pennsylvania. 44 cases were males and 9 females. Believes the sinus is embryonal ectodermal invagi-



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nation. Authors use methylene blue, dissect, and partially or completely close the wound. Johnston reported 3.6% post-sacral dimples in 1040 males examined from 1½ years to 58 years of age.

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ROENTGENOLOGY — RADIUM THERAPY — ELECTROSURGERY

ROENTGENOGRAPHY AND DIAGNOSIS

Branisteanu and *Moisuc* emphasize the importance of roentgenolic study of the intestinal mucosa. Normally the *plicae in the colon* are 5 mm. and their arrangement may be influenced by abnormal reflexes coming from diseased organs by way of motor fibers through the autonomic nervous system of the muscularis mucosa or by other reflexes. Normally they found a predominance of transverse plicae in the cecum, of oblique transverse plicae in the right half of the transverse colon and of longitudinal plicae in the descending colon.

Fiessinger and *Hutet* in a study of the normal colon in man state that the two extremities are constantly full due to the antiperistalsis and colonic mixing of fecal matter which gradually becomes of greater consistency low in the colon from its viscid state in the cecum. The sacculations may occur through normal tonic contraction or normal distention and are different in the spastic state. The study emphasized the considerable individual variation with time and bowel wall movement in any given case and emphasized the need for serial study.

Gershon-Cohen advises the routine use of the contrast air inflation roentgenogram and states that it is especially necessary in the diagnosis of early neoplasms, diverticulae, tuberculosis and inflammatory change of the mucosa.

Contrast enemas have gained importance abroad as well as in America. *Viamonte, Zdansky, Gershon-Cohen* and *Gillies* stress their importance.

Kuhlmann states that the colonray is most important in diagnosis and states that the tumor type cannot necessarily be identified in roentgenograms, whereas the infiltrating type can.

Pape emphasizes the importance of roentgenographic study in disturbances of motility in 224 pathologic cases studied.

Rother in an X-ray review of 546 cases of intestinal tuberculosis states that roentgen-examination is a more dependable diagnostic method than any other method. He stresses the importance of the fluoroscopic examination during the enema.

Zdansky states that transverse and longitudinal plicae of the mucosa must be accompanied by marked irregularity of contour to signify inflammatory swelling or lymphatic stasis. States that a comparatively frequent but usually disregarded finding in sigmoiditis is invagination, the same being confused with a circular stenosing tumor.

THERAPY

Chamberlain states that in general roentgen therapy of cancer is open to considerable improvement. The fractional treatment of Coutard and others is not necessarily as claimed to be the method of choice in all cases inasmuch as clinical experience plus a proper attention to the microscopic appearance of the biopsy specimen may lead to a better selectivity of cases. Preoperative irradiation is beneficial if it is followed by a sufficient delay for tumor regression. There is a decreasing emphasis on postoperative irradiation, however. Whether heavy radiation is beneficial requires further study.

Bensaude, Solomon and *Marchand* state that 50% irradiated fistulas are cured and 30% are markedly improved.



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Seven cases of chronic fissure-in-ano were cured by 3 to 6 irradiations. Partial improvement occurred in 3 cases and a failure in one case. Pain subsided in all cases. State that acute hemorrhoidal thrombosis is markedly improved with the duration of symptoms lessened by X-ray therapy. Whereas pruritus ani is "cured" by X-ray state recurrences are frequent. Advise it also in condylomas and suppurative proctitis.

Cilley, Leddy and *Kirklin* estimated the amount of radiation received by various operators during the routine course of colon roentgenoscopy during a period of several years and found that although multiples of the so-called tolerance doses were received, no injury occurred.

Duffy states that roentgen radiation is less efficacious than radium irradiation and should therefore be supplementary. Advises roentgen therapy as a preliminary procedure to surgery. In inoperable cases advises 18 to 28 days external irradiation depending upon the patients ability to withstand the treatment. Cites two rare cases where complete disappearance of the primary tumor occurred. Metastases occurred 4 and 7 years later.

RADIUM

Bensaude believes radium should be used only where diffuse growths are beyond surgical aid.

Binkley in a review of advanced carcinoma of rectum cases treated by radon seed implantation and external irradiation states that 24 cases were clinically symptom-free, 213 cases showed a moderate or minimal improvement, 155 cases showed greater improvement and only 8.5% were unbenefited. 25 cases treated with heavy radiation therapy showed results comparable with radical surgery.

Boxing discusses adenomyoma of the rectovaginal septum and advises radiotherapy preceding surgery if intestinal obstruction occurs by reason of size and states they should not be considered malignant and may be repeatedly observed over a period of time.

David reports 7 severe radium burn cases and concludes that when radium burn results in the treatment of carcinoma of the rectum carcinoma may still be present in the tissue requiring radical resection.

Gordon-Watson states that carcinoma containing undifferentiated cells should be radiated as they are much less resistant than those containing differentiated cells; and tumors of the anus are radiosensative and should also be radiated. He, however, despairs of the cure of rectal and large bowel carcinoma by radium because of the inherent resistance of the tumor. He states further that experimental work seems to indicate that the time required to inhibit and disintegrate a number of carcinoma cells in different stages of activity is not less than 7-10 days. The uniform intensity of radium as compared to the diminishing intensity of radon is responsible for the permancy of cures. In the same article Maisin reports that in 32 patients 100% were healed after 3 months and 57% were living with healed cancer of the rectum after 16-20 months. The method of radiosensitization followed by Coutard's method of roentgen irradiation was used.

Lockhart-Mummery agrees with Gordon-Watson excepting that he does not believe adenocarcinoma is any less radio sensative than squamous celled carcinoma.

Schreiner reports on the successful irradiation of 8 cases of inoperable rectal carcinoma treated from 1919-1929. External irradiation combined with glass seeds and filtered radon were used.

An outstanding article is that of *Shedden* who concludes that with radium treatment in the properly selected case early growths can be destroyed, clinically inoperable cases can be rendered operable, and the worst and more advanced cases can be rendered more comfortable. States that the



Reducing Fecal Toxicity

Whenever the bowel loses its normal selectivity and the liver's ability to detoxify is overtaxed, a flood of toxic material enters the system

Soricin detoxifies at the port of entry—the bowel

Soricin is not a panacea—it is merely an effective means of decreasing toxic absorption from the enteric tract.

Soricin inhibits putrefaction and abnormal bacterial proteolysis.

The continued use of Soricin aids in desensitizing the patient who has become sensitized to the autolysates of his intestinal flora.

Specifically, Soricin is useful in the treatment and prevention of:

Bacterial hypersensitivity of the intestinal tract
"Irritable colon"
Intestinal toxemia
Allergic diarrhea
Urticaria
Non-ulcerative colitis.

Consequently, Soricin is of value in the relief of many symptoms such as headache, vertigo, anorexia and migraine.

SORICIN DOSAGE FORMS:

Soricin Capsules: Enteric capsules of sodium ricinoleate available in five-grain and ten-grain sizes.

Soricin Tablets: Enteric coated tablets each containing five grains of sodium ricinoleate.

ACTION:

Detoxifies in vivo Desensitizes Inhibits putrefaction Prevents toxic absorption

LITERATURE AND SAMPLE ON REQUEST

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radio-surgical technic of Neuman and Coryn was reported on unfavorably at St. Marks and needs further study. Further research is necessary to determine the correct dosage and factors influencing the same. Whereas there are a number of 5 year cures the author believes that there are too few cures to warrant anything but surgery in operable cases.

Shepley advises preoperative irradiation.

ELECTROSURGERY

Bowing and *Fricke* report on 58 cases of rectal cancer treated between 1930 and 1933 by radium application and aided by surgical diathermy. Radical excision followed 37 cases. 27 cases appear free from recurrence. In 3 cases no evidence of carcinoma was seen in the surgical specimen removed, and in 3 others most of the cells were found destroyed.

Electrocoagulation has received more favorable attention and *Fansler* states that in cases unable to withstand radical surgery in inoperable obstructive growths, particularly where the growth produced distressing symptoms, and in early low grade malignancies where flat button-like 1 cm. or less sized lesions or tumor with a pedicle are present electrocoagulation is indicated.

Wadhams and *Carabba* performed 15 consecutive anastomoses of the intestine in animals successfully using a bipolar coagulation current of 1000 milliamperes.

Yoemans reviews the cancer cases seen at the New York City Cancer Institute during the past 10 years and states that the good results obtained by electrosurgery combined with radon seed implantation in apparently hopelessly advanced lesions is of great interest. Relief of pain is also obtained by chordotomy, and alcohol subarachnoid injection.

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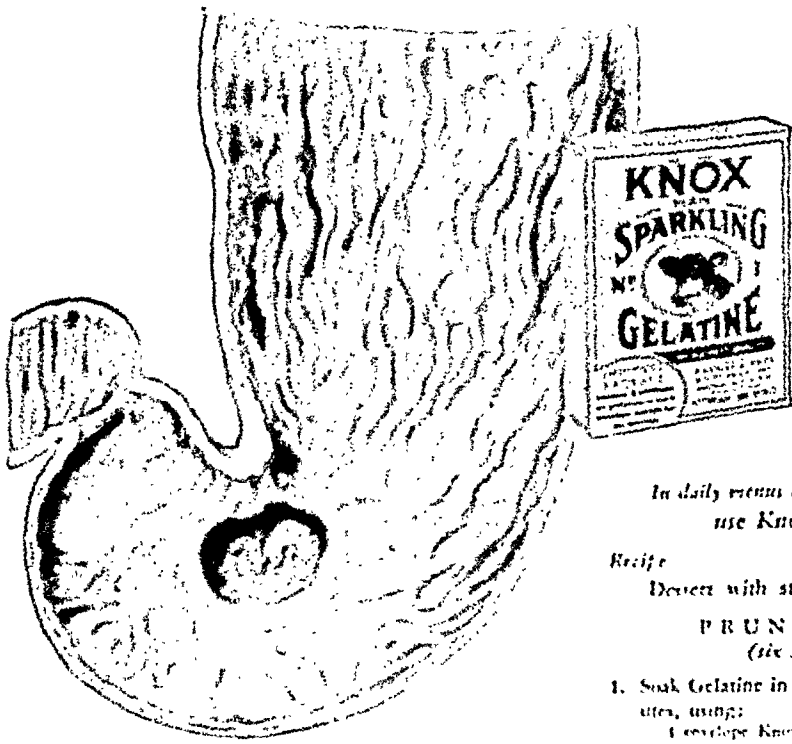
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When advising a diet for gastric disturbances, remember that Knox Gelatine (U.S.P.) is a valuable vehicle. Knox Gelatine is not only an easily digested protein but blends with whatever foods are allowed into tempting salads and desserts.

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Recipe

Dessert with strained prune pulp.

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(six servings)

1. Soak Gelatine in cold water about 5 minutes, using:
   1 envelope Knox Sparkling Gelatine
   ¼ cup cold water
2. Add to the following, stirring thoroughly:
   ¼ cup hot prune juice
   1 cup cooked prune pulp
   2 tablespoonfuls lemon juice
   ⅔ cup sugar
   ¼ teaspoonful salt
3. Cool. When mixture begins to thicken, *fold in:*
   2 egg whites, stiffly beaten
4. Rinse mold or dish in cold water, and fill with dessert. Chill. To serve, unmold and garnish with whipped cream, or serve with custard sauce.

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TUBERCULOSIS OF THE COLON AND RECTUM

Augé reports a case where an amoebic ileocecal mass closely simulated tuberculosis.

Chisholm and *Gauss* write an excellent paper reviewing the findings in 71 proven or probable cases of anorectal tuberculosis. They find the incidence of anorectal complications in pulmonary tuberculosis to be 3 to 5 per cent. Diagnosis should be by guinea-pig injection of emulsion prepared from pus scrapings or tissue material, or else by suitable culture growth. The treatment should be surgical and proved most gratifying in 70 of the cases.

Gomez and *Rubio* have an excellent paper reviewing the clinical, roentgenologic, proctoscopic and necropsy studies of the large bowel in 500 patients with pulmonary tuberculosis. Air inflation enemas were used. Ulcerations hypertrophy of the ileum, edema of the submucosa, and proximal colitis granulosa were found.

Granet reviews 2086 cases of pulmonary tuberculosis and finds an incidence of 37% with intestinal tuberculosis. 86% showed cecal involvement. Only 2 out of 150 consecutive sigmoidoscopic examinations showed tuberculous ulcers of the rectum. Roentgenographic findings were correct in 43 of 49 autopsies. 95.4% of the intestinal cases had pulmonary cavitation.

Konjetzny describes an ulcerative ileitis of tuberculous origin resulting in narrowing of the lumen and tubular thickening of the wall.

Several authors checked on the Triboulet reaction in intestinal tuberculosis. *Robinson* and *Gruickshand* review 109 cases and found no diagnostic value. *Tisell* states it is of no value for early diagnosis.

Rother writes an extremely interesting paper and valuable partly because of the wealth of material studies. 546 cases were seen and their various findings described. The ileocecal region is of primary importance in the diagnosis.

Santy advocated heliotherapy and ultra violet radiation in the treatment of intestinal tuberculosis and would combine unilateral surgical exclusion with this rather than bowel resection by reason of the results seen in two series of 10 patients each.

Watson and *Hewitt* state that 10 years experience has convinced them of the efficacy of the quartz mercury vapor lamp. Supplementary treatment with diet (high vitamin-low residue) rest and fresh air is necessary. The associated pulmonary condition must not be too far advanced.

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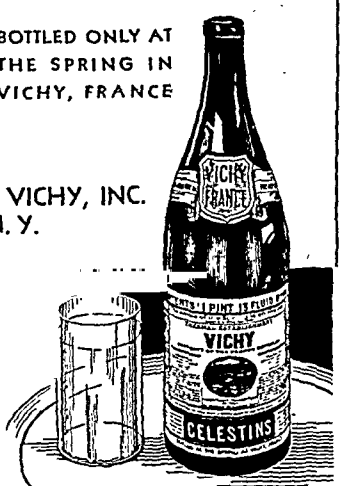
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Because of its antacid properties, Vichy Celestins has been found useful for gastro-intestinal toxemias, particularly those of the fermentative type. In disturbances due to overeating, faulty diet or alcoholism, Vichy Celestins also has a marked corrective influence.

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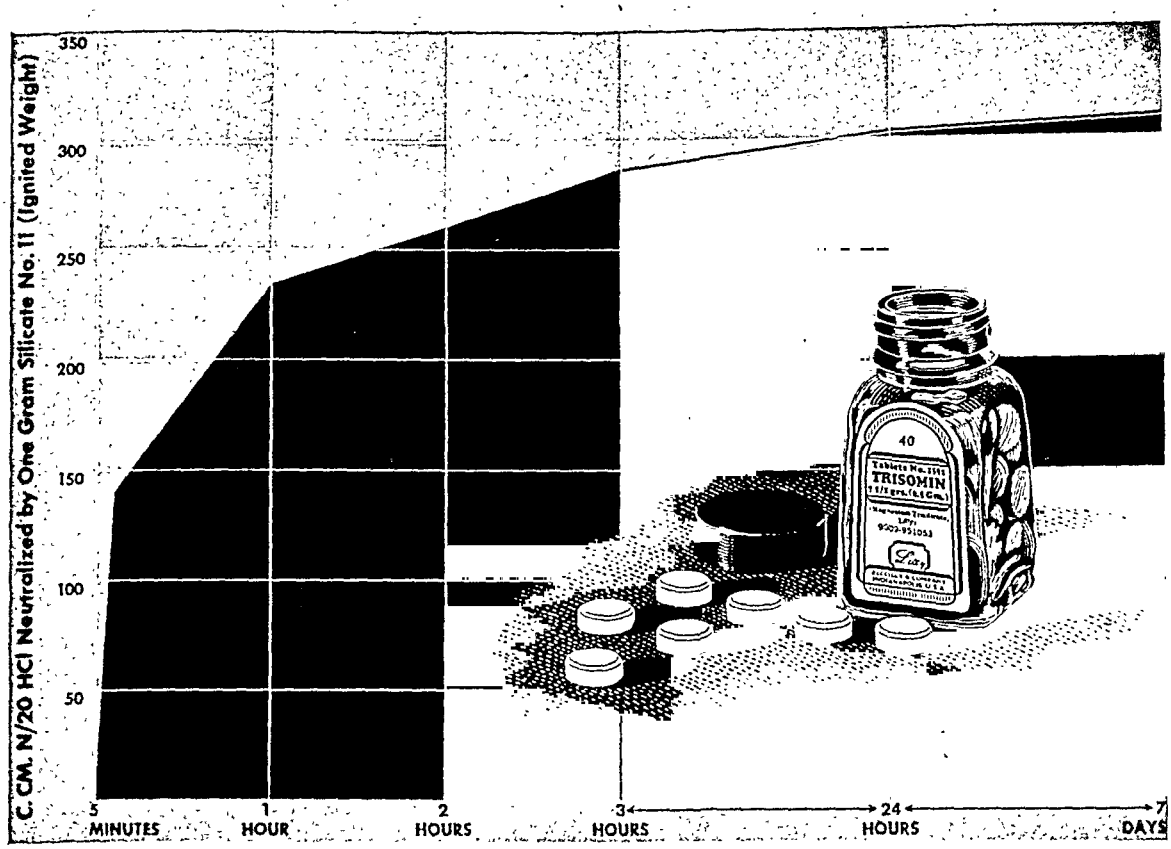
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● As shown by Mutch, synthetic magnesium trisilicate effectively neutralizes acid and displays a prolonged action in accomplishing this purpose. It is also a powerful adsorbent of alkaloids, putrefactive amines, bacterial toxins, and food poisons. Relatively large doses may be given by mouth since the compound is nontoxic. 'Trisomin' is not absorbed from the gastro-intestinal tract and alkalosis is not a probable side effect.

Tablets 'Trisomin' (Magnesium Trisilicate, Lilly), 7 1/2 grains, are supplied through the drug trade in bottles of 40 and 500.

Literature concerning dosage will be supplied to physicians upon request.

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"CONNOTATIONS." By H. J. Sims, M.D., Denver, Colorado.

Since Hunt and Taveau, in 1906, observed the vasodilator effect of choline esters, considerable attention has been given to aceteylcholine as the chemical mediator of parasympathetic nerve impulses.

In 1880, the pharmacologist, von Anrep, discovered the local anesthetic properties of cocaine. In 1884, Koller reported his experimental and clinical results in surgery of the eye. The term, "spinal anesthesia" was introduced by Corning in 1885. Bier, in 1889, first injected cocaine intraspinally.

Bastianelli, in 1890, reported three cases which presented symptoms similar to those now recognized as "liver deaths," a syndrome first described by Heyd.

Claude Bernard, in 1855, expressed the view that, in addition to the external secretions which are derived from the blood; the glands produce internal secretions which are derived delivered to the blood. To him belongs the origin of the term, "internal secretion."

Theophile de Bordeu wrote, in 1775, "Every organ serves as a workshop for the preparation of a specific substance which enters into the blood; and that such substances are useful to the body and are needed in order to maintain its integrity."

Metchnikoff (1845-1916) was a biologist and not a pathologist. He was engaged in zoological research when he discovered the mechanism of intracellular digestion in the mesodermal cells of lowly animals.

De Garcia, a singing master of London, is credited as having invented the laryngoscope.

The first thermometer for recording body temperature was used by Traube, in 1850. The thermometer was slightly over ten inches long and required thirty minutes under the axilla to register.

Reginald Fitz, in 1899, wrote, "Acute pancreatitis is to be suspected when a previously healthy person, or sufferer from occasional attacks of indigestion, is seized with violent pains in the epigastrium, followed by vomiting and collapse, and in the course of twenty-four hours, by a circumscribed epigastric swelling, tympanitic or resistant, with a slight rise in temperature."

Cooper, of England, in 1903, described acute dilatation of the stomach in a child eleven months old. The child previously healthy, while playing, suddenly seemed to stop breathing. He "made a noise in the throat" and died in a few minutes without a struggle or a convulsion. Autopsy showed a dilated stomach containing nineteen ounces of Mellins' Food. A stomach at this age should hold only about nine ounces.

Moor, in 1881, confirmed the theory that tuberculosis may cause cirrhosis of the liver.

Steatosis, which occurs so often in tuberculosis, was recognized by Andral in 1829.

McNeal is thought to have first recognized carcinoma of the bile ducts in 1835.

In 1821, Caindent advised the use of iodine in the treatment of syphilis. Wallace, of England, in 1825, is credited with the use of potassium iodine in syphilis.

Claude Bernard experimentally produced hemorrhagic pancreatitis by injection of bile and sweet oil into the pancreatic duct. The method by which diseased gall bladders predispose to pancreatitis was suggested by Opie in 1901. From his experimental work, he concluded that a gall stone lodged at the ampulla of Vater might convert the choledochus and the duct of Wirsung into a common channel.

Wren, in 1656, injected an infusion of opium into the vein of a dog and obtained narcosis. In 1823, Hale described the injection of castor oil into his own vein.

TRI-CALSATE



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Extensive clinical experience proves the definite superiority of Tri-Calsate in the treatment of hyperchlorhydria and peptic ulcer.

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As no carbon dioxide is evolved during the reaction in the stomach, gastric distention and belching are eliminated.

Tri-Calsate is non-toxic and non-irritating. The probability of gastro-intestinal irritation is remote. The kidneys are unharmed. Patients like it because it is palatable and gives rapid relief without distressing systemic effects. Economical, too.

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Hayden, in 1855, injected a solution of sodium chloride into the vein of a patient with cholera. Haford injected a solution of ammonia intravenously into a patient bitten by a snake.

Cotton, in 1917, gave the first report of cholecystitis due to B. aerogenes-capsulatus.

Riedel, in 1888, first called attention to enlargement of the right lobe of the liver in cholelithiasis.

The introduction of rubber gloves, as a surgical requirement was not enthusiastically received. Several types of elastic varnishes to cover the hands were suggested in preference to gloves.

Torsion of the fallopian tube was reported by Bland-Sutton in 1890.

Talma of Utrecht was the first to suggest establishing a collateral circulation by means of adhesions between the abdominal viscera and the parietes for the relief of ascites in cases of cirrhosis of the liver. The first operation by Van der Meude, in 1889, and another by Schelkly, in 1891, resulted in death. Lens, in 1892, repeated the procedure and the patient lived six months.

Vautrin, of Nancy, was probably the first to propose eversion of the tunica vaginalis in the treatment of hydrocele. Doyen claimed priority.

Mayer, in 1860, removed the first sarcoma of the uterus. Virchow made the microscopic report. In 1871, Kreegar was able to collect nine reported cases.

Schneck, in 1811, first recognized the difference between massive collapse of the lungs and pneumonia. Partial collapse of the lungs was described by Alderson in 1830. He recognized the condition in four fatal cases of whooping cough. The relationship of bronchial tube obstruction to atelectasis was noted by Traube in 1836. He believed conditions, other than mechanical, were more important factors.

Mendelssohn, in 1841, experimentally produced the condition in dogs.

Gardner, of the University of Edingburgh, advanced the opinion that a mucus plug obstructing the bronchi, represented the basic etiology.

Bartels, in 1860, confirmed the findings of Gardner.

Pasteur, in 1886, described the clinical symptoms.

Sewall, of Denver, in 1921, was the first in America to describe the pathology.

Balliou, (1538-1616), physician to Henry IV, first described whooping cough in 1578. During his life time he introduced the term, "rheumatism."

Reply to a recent Editorial: "The Desirability of Measuring the Acidity of the Gastric Secretions Rather Than That of the Gastric Contents." By A. Galambos, M.D., New York.

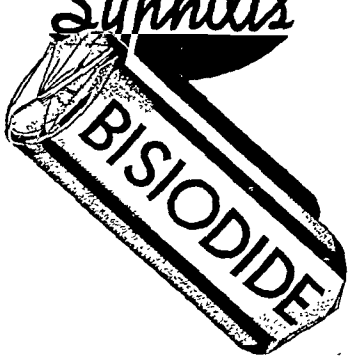
Your Editorial, in the August issue, entitled: "The desirability of measuring the acidity of the gastric secretions rather than that of the gastric contents," from the pen of C. M. Wilhelmj, M.D., serves as an occasion to call attention to a paper of mine, which may readily answer the Editorial.

My paper, entitled: "Direct Examination of the Gastric Juice, a New Functional Test," appeared in the Archives of Internal Medicine, in the November issue of 1926 (Vol. 38, pp. 654-662) and deals, as its title indicates, with the question discussed by the Editor. The same question which has been brought up today, as a "desirability," has been discused and answered in the affirmative, 12 years ago by the writer of these lines.

I fully concur with the Editor, when he states: "that the acidity of the GASTRIC CONTENTS can not be used to study changes in the acidity of the GASTRIC SECRETIONS; the two are distinct entities and should be measured separately."

The Editor after discarding the use of histamin for such studies, concluded by recommending: "a better way of

Oral TREATMENT OF Syphilis



Bisiodide

An organic compound, being a synthesis of Bismuth (25%) and organic Iodine (58%). Indicated in all stages of Syphilis. Used concurrently with arsenicals in primary and secondary stages; exclusively in tertiary stages. Supplants intramuscular injection treatment.

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Impressive experimental evidence indicates that the most important factor in the control of gastroduodenal hemorrhage is the protection of the newly formed clot in the bleeding vessel. By raising the pH of the gastric contents above that at which pepsin is active, the protective clot is permitted to remain in situ, undigested.

In a recent series* employing the continuous drip method, 21 cases of severe gastroduodenal hemorrhage were successfully treated without mortality.

Creamalin — the distinctive colloidal cream of aluminum hydroxide —neutralizes 12 times its volume of N/10 HCl in less than 30 minutes. Within the stomach, it produces virtual anacidity, rendering pepsin inactive and insuring the safety of the protective clot. Creamalin produces no secondary rise in HCl secretion, and since it is amphoteric, cannot lead to alkalosis or change in blood pH values.

Because of the soundness of the underlying principle of Creamalin therapy in ulcer hemorrhage and the satisfactory results obtained by this method, Creamalin should be the therapy of choice when hemorrhage due to ulcer presents itself.

*Woldman, E. E.: The Treatment of Hematemesis and Melena by Continuous Aluminum Hydroxide Drip. Am. J. Med. Sci., 194: 333 (Sept.) 1937.

Reprints of this and other recently published articles dealing with Creamalin, together with sample, will be sent to physicians on request.

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THE SUCCESSFUL ULCER TREATMENT

studying the acidity of the gastric secretions by putting some substance which is not destroyed or absorbed from the stomach in the fluid of the test meal and to determine the concentration of this substance in the gastric samples. When this is known, it is possible to say just how much of the fluid in the sample of gastric contents is fluid originally given with the test meal and how much is fluid of the secretions which entered the stomach. By dividing the acidity of the contents by the amount of fluid secretions which they contain, the true acidity of the gastric secretions can be obtained."

This recommendation as much as it is commendable and desirable, remains as a "pium desiderium" as long as the Editor fails to mention, what is this "better way," and what is "the substance, which is not absorbed or destroyed, etc." Whether or not the Editor knows of some such ways and means, or he merely wishes to express the desirability of having such methods at our disposition, can not clearly be seen.

At this point may I make reference to my above mentioned paper, which anticipated your questions and gave an "a priori" answer. I, likewise, have found desirable and important to have a method of obtaining and examining the DIRECT GASTRIC JUICE, instead of the GASTRIC CONTENTS in 1925. I have found, that "with the advent of the Rehfuss' tube we have a means that enables us to make examination of the gastric content by a fractional method and it becomes possible to make routine study of the fasting stomach, investigating the gastric juice—its secretion, concentration and amount, as well as its influence, psychic or otherwise—very much as may be done in animal experimentation by means of fistulas or the Pawlow pouch."

After comparing my method of providing for and obtaining unadulterated gastric juice for analysis or other purposes with other, more complicated and less applicable methods I concluded by recommending my simple method "its performance being even more simple than the administration and examination of a test breakfast."

In the method, advocated: "the Rehfuss' tube is introduced into the fasting stomach and its content withdrawn by means of a perfectly tight syringe. The tube is then left in place. As the gastric juice accumulates it is withdrawn at predetermined intervals—three, five, ten, fifteen minutes—and the quantity and total acidity of each portion is separately determined. Any special examination, microscopic or otherwise, can be performed at the same time on any or all of these samples.

Insofar as my examination of the literature has extended, no such test has heretofore been recommended, either to complete the functional food tests in common use, or as a substitute for them, when it is desirable to obtain pure gastric secretion, unadultered by food, a procedure, which, as has been pointed out by Compton, would open up a wide field of study in relation to gastric function."

When the Rehfuss tube remains in the stomach, the presence of its tip will excite and maintain the process of gastric secretion. The acid-concentration and the amount of the gastric juice widely varies according to the underlying conditions. The method best adapts itself for conditions with concomitant hyperacid or hypersecretory disorders. In such states huge amounts of gastric juice can be obtained, with high concentration of its HCl content. The highest concentration is observed as a rule after the first 5 or 10 minutes. After a period of continuous secretion of ca. 30 minutes, a respite sets in, which is followed again by the resumption of a renewed secretory period. After a second secretory activity of 30-60 minutes duration, an inhibition of the gastric secretion sets in, sometimes for a period of hours.

The method as described and illustrated by various curves, showing the variations under pathological conditions, as well as also the normal variations with the same individuals, under normal conditions, is very plain and simple. It requires only a Rehfuss tube, which will on fasting be introduced in the stomach and kept in situ, for the required period of examination or observation. The samples received at any required interval, give fairly accurate record of the actual gastric secretion. The juice received is the unadultered, pure gastric juice, and not the food containing gastric content, as is generally used for examinations and tests.

For further informations I wish to refer the reader to the original article. I must remain content at this time to have called attention to an actually existing method of approach to the problem in question.

APPENDICITIS

Blood counts were recorded on 6,601 cases; of these, 65 showed a leukopenia of which 59 were in the chronic group. Five deaths occurred in this group. In 3,086 cases there was a leukocytosis of 5,000 to 10,000 with 59 deaths; in 2,265 cases there was a leukocytosis of 10,000 to 15,000 with 43 deaths; in 1,031 cases a leukocytosis of from 15,000 to 25,000 with 124 deaths; and in 174 a leukocytosis of 25,000 to 50,000 with 49 deaths. It was also found that the mortality rate decreased with the elevation of the mononuclear cells and vice versa.

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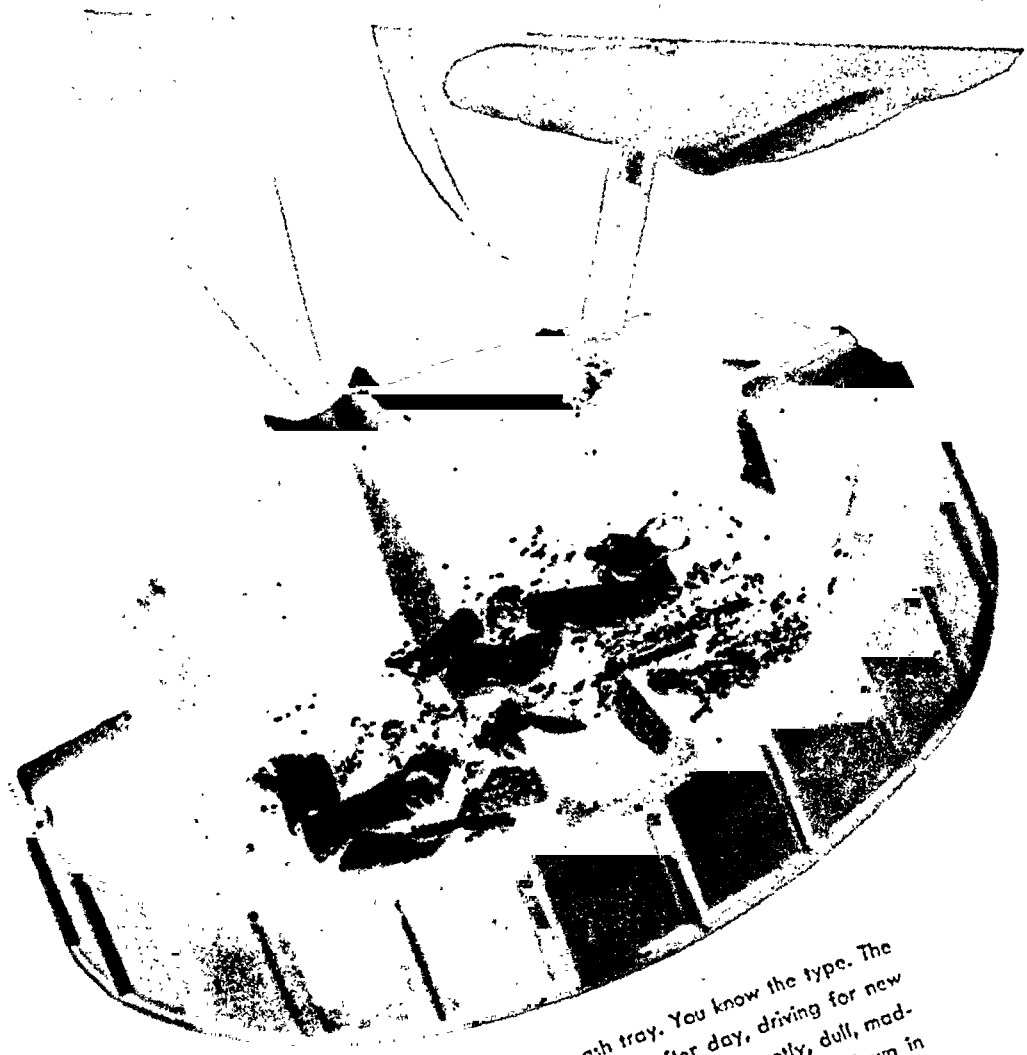
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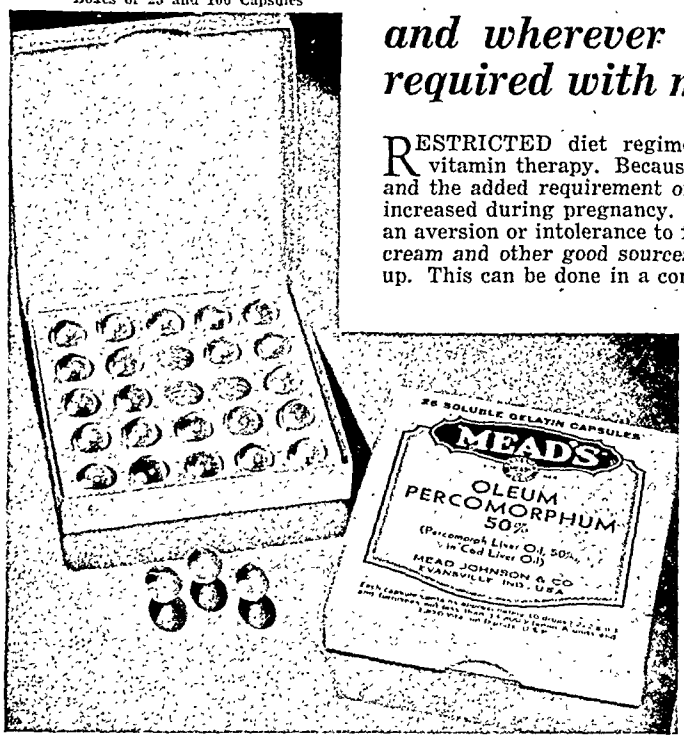
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Adrenal Cortex and Intestinal Absorption*

By

PROF. DR. F. VERZAR
BASEL, SWITZERLAND

THE editors of this Journal have been kind enough to ask me for an account of recent work in my laboratory. For ten years I have worked with my collaborators on the question of absorption from the intestine. We made it our task to study especially those cases of absorption which seem to be directly opposed to the established laws of diffusion osmosis and filtration which ordinarily govern the process of absorption (1).

Such a case is, for example, the absorption of certain sugars. Glucose and galactose, the sugars which play a special rôle in metabolism, are absorbed especially well, in fact three to four times more quickly than are other hexoses of equal molecular weight, such as mannose and sorbose, or pentoses, such as xylose, arabinose and ribose (2). While the latter sugars are absorbed in accordance with the laws of diffusion, the former are not. The absorption of the latter is greater the greater the concentration of the solution, while with the former sugars, no matter what the concentration the same quantity is always absorbed in a given time, and this represents the maximum amount which can pass through the membrane (3).

To explain this difference a special activity of the intestinal mucosa was postulated. It could be shown that this activity was particularly strong in the jejunum, in comparison with the lower parts of the small intestine (4), and that it could be influenced by the pH (5) of the intestinal contents, and inhibited by low temperatures (6) and by iodoacetic acid (7). This last fact gave us a hint as to what the process might be. We know from the influence of this substance on muscle metabolism that it interferes with oxidation-reduction processes connected with the resynthesis of hexose phosphoric acid during the recovery process in the muscle. We therefore supposed that a similar transformation of glucose (and galactose) might occur in the cells of the intestinal mucosa, and that this process might be stopped by iodoacetic acid. Such a synthetic process in the mucosa would maintain a high diffusion gradient between the sugar in the intestinal lumen and that in the mucosal cells by constantly transforming the sugar which diffuses into the mucosal cells into another substance. This might be the explanation for the rapid absorption of these sugars.

I do not want to refer to all the details of older work, but I may say that it was not by accident that we one day postulated, as a working theory, that the adrenal cortex might influence this synthetic process (8). We know that the muscular weakness, so well known to all who have studied the effect of destruction of the adrenal cortex, is caused by a lack of the restoration processes in the muscle. We had shown an elongation of the contraction curve of a single muscle twitch in adrenalectomized frogs and rats (9), and we had also shown a lack of carbon dioxide and lactic acid formation (10), so that it was logical to test the effect of extirpation of the adrenals on the activities of the intestinal mucosa.

It was immediately seen that the activity was abolished by adrenalectomy, and that glucose was then absorbed with about the same velocity as xylose. An injection of cortical hormone restored the rate of the glucose absorption to four times that of xylose (11).

We next showed that fat absorption was also destroyed by adrenalectomy and was restored by the giving of cortical hormone (12). Further, lactoflavin, or provitamin B_2, which in the normal animal probably has to be transformed in the intestinal mucosa to flavin phosphoric acid (vitamin B_2) to give the so-called "yellow breathing ferment" of Warburg, is not phosphorylated if the adrenal cortex is removed (13).

Our work on intestinal absorption thus brought us to studies on the function of the adrenal cortex. In studying absorption from the intestine one has a good opportunity to study the activities of a single cell layer, such as is found in the absorbing epithelium of the intestine. These studies showed us that in adrenalectomized animals a series of syntheses (esterifications) are lacking, namely the phosphorylation of glucose, the synthesis of fat, which probably goes via the phospholipids, and the phosphorylation of lactoflavin. Since such processes are not only of importance for absorption but also for other metabolic activities, the disturbances in a cortico-adrenalectomized animal are very complicated. The lack of the restoration processes in the muscle is easily explained by the inhibition of phosphorylation. A new step was the discovery that the wandering of fat from the fat depots to the liver is only possible in the presence of the cortical hormone (14).

Furthermore, disturbances in carbohydrate metabolism cause important secondary disturbances in osmotic conditions, so that water and sodium metabolism are also disturbed. Then the inability to synthesize the allimportant "yellow breathing ferment" must influence the whole intermediate metabolism of an animal in the most fundamental way.

Recently we were able directly to show that adrenalectomized rats and cats lose the capacity of transforming lactoflavin into flavinphosphoric acid in the liver (15). It was also shown that adrenalectomized rats could be kept alive with flavin phosphoric acid from liver or yeast, and that all the absorption disturbances could be healed with this substance (16). Thus the metabolic disturbances in adrenalectomized animals may be largely due to the inability to synthesize the "yellow ferment."

Unexpectedly we were pushed into questions of more practical importance through these experimental results. The question inevitably arose whether in

*From the Physiological Laboratory of the University of Basel, Switzerland.
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human pathology any symptoms are known which might be caused by a disturbance of the activity processes in the intestinal mucosa, and whether the adrenal cortex plays any part in these disturbances.

By chronic poisoning of a young animal with iodoacetic acid (a poison whose action is in many ways comparable with lack of adrenal cortex), we were able to produce an illness which reminded us in all its details of Gee-Herter's disease or the celiac disease of children. The animals stopped growing, they had an enlarged abdomen, steatorrhea, osteoporosis and hypochromic anemia (18).

Now, celiac disease in children seems to be identical with the so-called "nontropical sprue" or "idiopathic steatorrhea" of adults, a disease to which attention was called about five years ago, and which is now found everywhere in Europe (19). A great loss of strength with bulky stools containing large quantities of fat are characteristic of this disease, and in the later stages a darkening of the skin develops, as in Addison's disease. A study of these cases often reveals a history running back ten years or more of slight unexplained intestinal disturbances. I am convinced that many such cases of uncertain origin are cases of disturbances of the special activity process in the intestinal mucosa due to insufficient production of the adrenal cortical hormone.

I should like to suggest that these milder illnesses, of which the cause is unknown, the Gee Herter's disease in children and "nontropical sprue" in the adult, should all be looked on as possibly "adrenocortical disturbances of absorption," or since the adrenal cortex is called the "interrenal body," one might preferably speak of "interrenal disturbances of absorption," or "interrenal steatorrhea."

We may note that it is only accidentally that doctors first notice the steatorrhea in these illnesses. Glucose absorption is also disturbed in all these cases, but the sugar does not appear in the feces because it is fermented in the large intestine by bacteria.

These cases often respond marvelously to liver extracts (as Castle has shown), and to such yeast extracts as contain undestroyed flavinphosphoric acid. The liver extracts contain this substance. Yeast extracts on the contrary often do not contain this easily destroyed substance. At present it is unfortunately impossible to give patients adrenocortical hormone in quantities, which, judging from animal experiments, could be expected to be effective.

In cases of steatorrhea, a primary disturbance of absorption should be diagnosed only if one can be sure that the work of the digestive enzymes and intestinal motility is normal. However, one must not suppose that sugar or fat are not absorbed at all in these cases. Even total adrenalectomy abolishes only some special processes whose function it is to speed up the absorption of certain substances. The absorption of fat and glucose still continues but at a much reduced rate.

One must not expect every patient with Addison's disease to show disturbances of absorption with steatorrhea. Pigmentation in this illness seems to be the result of a hypofunction of the adrenal medulla while disturbances of absorption and loss of strength are the result of disease of the cortex. It is true that in the later stages of "nontropical sprue," the adrenal medulla also seems to become affected and pigmentation results. One might think of Addison's disease as starting in the adrenal medulla and Gee-Herter's disease and "nontropical sprue" as starting in the cortex. Many cases are now known in which Addison's disease seemed to change into sprue and vice versa (20).

It may be that hypofunction of the adrenal cortex is to be found in the absence of characteristic anatomical changes. Perhaps there may be only a decrease in the volume of the organ. Unfortunately there have been as yet, but few postmortem studies made to answer this question.

The physiologists' work must generally be uninfluenced by practical considerations, in order that he may investigate his problems as fundamentally as possible. But it is rather fortunate if, as in this case, one is forced to connect theoretical results with the experiences of the clinician.

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The Physiological Control of Gastric Acidity*

By

CHARLES M. WILHELMJ, M.D., REX W. FINEGAN, M.D.

and

FREDERICK C. HILL, M.D.

OMAHA, NEBRASKA

DURING the past six years this laboratory has been engaged in a detailed study of the physiological factors regulating gastric acidity, particularly in an attempt to evaluate the relative importance of the various mechanisms involved. In the present summary technical details and descriptions of the various control experiments will be omitted and only the general conclusions will be given.

GENERAL METHODS

Two types of test meals were used in the various phases of the work. *A tenth normal hydrochloric acid test meal* with and without histamine stimulation was used to study the factors responsible for the lowering of the acidity of the gastric contents and the amount and composition of the non-acid secretions which may enter the stomach. *A specially prepared 2 per cent Liebig's extract test meal* was used to study the gastric secretory curves under various conditions. Both types of test meal contained 15 mg. of phenol red per liter, and the determination of the per cent of phenol red in the gastric samples enabled us to say just how much of the fluid in the gastric samples was fluid of the test meal and how much was fluid of the various secretions which entered the stomach. It was thus possible to study the acidity of the secretions entering the stomach as well as the acidity of the gastric contents. It was also possible to estimate in the total fluid secretions entering the stomach the size of the two fractions representing the acid secretion and the non-acid secretions. The latter is sometimes spoken of as the diluting fluid.

I. THE STRENGTH OF THE ACID SECRETED BY THE STOMACH

We believe that it is now well established, due largely to the work of Hollander (1, 2, 3, 4), that the strength of the acid secreted by the stomach is practically a physiological constant. In dogs the value for the pure acid secretion is approximately 0.170 normal (600 mgm. of acid chloride per 100 c.c. of secretion). This value remains constant, uninfluenced either by the amount of acid secreted or by the acidity of the material already in the stomach. Since hydrochloric acid of this strength is damaging to living tissues, it is fortunate that the acidity of the mixed gastric secretions, under normal conditions, seldom reaches this value. This paper deals with the various factors which bring about the necessary dilution and neutralization.

II. DECREASE IN ACIDITY DUE TO DILUTION AND NEUTRALIZATION

Over 220 fractional gastric analyses have been made on 34 normal dogs, while using the 2 per cent Liebig's extract test meal. In about 90 per cent of these analyses the gastric secretory curve showed a striking uniformity. The characteristics of this commonly seen normal curve are as follows: The quantity of total fluid secretions entering the stomach, per 100 c.c. of gastric contents, increases progressively from the beginning of the experiment until the stomach empties. The composition of the total fluid secretions shows rather constant variations during the different phases of the secretory curve. The quantity of acid fluid is low at the beginning but rises rapidly so that near the middle of the curve there is usually more acid than non-acid fluid present in the gastric contents. Near the end of the curve, just before emptying occurs, the secretion of acid fluid becomes much slower and the curve may actually fall off. With this there is an abrupt and marked relative increase in the amount of non-acid fluid entering the stomach. The acidity of the total secretions entering the stomach shows corresponding changes; the curve rises rapidly at first but near its middle or end there is a cessation of the rise, or more commonly, an abrupt fall. Coincident with the terminal increase in the inflow of non-acid fluid and the fall in the acidity of the total secretions, bile appears in the gastric samples.

One of the first questions which we attempted to answer was: What is the source of the non-acid fluid which gushes into the stomach just before emptying occurs? Is it of intragastric or duodenal origin? Experiments were first performed on whole stomach pouches isolated from the duodenum. When fractional analyses, using the Liebig's extract test meal, were performed on juice from these pouches, the secretory curves were strikingly different from those obtained in the intact stomach connected to the duodenum. The increase in non-acid fluid failed to occur as the pouch emptied; in fact this secretion often decreased to zero, apparently as a result of this the acidity of the secretions rose progressively during the experiment and finally reached the value of the pure acid secretion or even surpassed it. From this it appeared that the marked increase in non-acid fluid, so characteristic in the intact normal stomach, is not of intragastric origin but must be due to regurgitation of fluid from the duodenum.

Certain hypothetical objections were brought up against these experiments on whole stomach pouches and in order to meet them a series of experiments were performed on dogs before and after performing the Mann-Williamson operation of "surgical duodenal drainage." In this operation the duodenum is detached from the stomach and the upper end closed, the lower end is drained into the terminal ileum, and the jejunum is brought up to the stomach to take the

*Departments of Physiology and Experimental Surgery, Creighton University School of Medicine.

Submitted May 30, 1937.

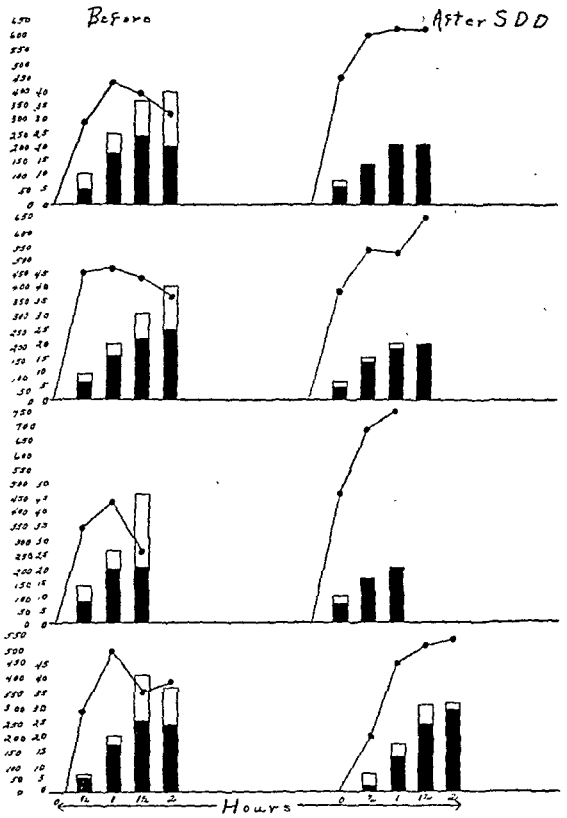


Fig. 1. Shows the average gastric secretory curve obtained with four dogs *before* and *after* the Mann-Williamson operation of "surgical duodenal drainage."

The height of the rectangles shows the total amount of fluid secretions entering the stomach per 100 c.c. of gastric contents. The *black* portion indicates the fluid of the acid secretion and the *white* portion the fluid of the non-acid secretions. The line represents the acid chloride concentration of the total secretions entering the stomach.

The scale increasing by 5 represents the fluid of the secretions per 100 c.c. of gastric contents, and the scale increasing by 50 represents the acid chloride per 100 c.c. of secretion entering the stomach.

Samples were removed from the stomach every half hour.

place of the duodenum. Following this operation the average secretory curves were exactly the same as those found in whole stomach pouches. The acidity of the secretions entering the stomach after operation was always markedly higher than before operation; the non-acid fluid was very small in amount, and it tended to *decrease* even to zero rather than to *increase* as the stomach emptied (Fig. 1).

In further experiments on whole stomach pouches a tenth normal hydrochloric acid test meal was used and it was found that the isolated stomach had very little ability to reduce the acidity unless the amount of acid present was very small. A more detailed study showed that the amount of non-acid fluid secreted by the isolated stomach was small in amount, that it was secreted at nearly a constant rate, independent of the rate of acid secretion, and that marked and abrupt increases did not occur.

The results of the above experiments were clear-cut and definite, and showed clearly that regurgitation of duodenal secretions is a normal event, occurring as the stomach is emptying, and that the primary effect of regurgitation is to prevent further rise, or more commonly, to lower the acidity of the *total secretions* entering the stomach.

A detailed study was next made of the *duodenal* secretions and it was found that the alkalinity of the mixed secretions might vary from 0.01 to 0.07 normal, apparently depending upon the amount of pancreatic juice which was mixed with the bile and succus entericus. The average value in nearly one hundred analyses was found to be 0.04 normal alkali. From this it is evident that the efficiency of the duodenal *secretions in lowering the acidity* of the gastric secretions depends more upon dilution than upon neutralization.

III. THE PHENOMENON OF ACID INHIBITION

The second factor in the physiological control of gastric acidity is one to which we have given the name "acid inhibition." This mechanism acts *in the stomach* to control the intragastric chemical phase of acid secretion and *in the intestine* to control the intestinal phase of acid secretion.

(a) Intragastric acid inhibition. When the acidity of the gastric contents rises above a certain threshold value progressive inhibition of acid secretion occurs and at certain concentrations acid secretion may be totally inhibited. This mechanism is entirely an intragastric one and apparently does not involve the vagus nerves since it occurs in the vagally denervated whole *stomach isolated from the intestine.* The exact level of acidity at which inhibition begins varies in different animals but it is usually not marked until the acidity of the gastric contents approximates 60 units (0.06 normal acid). Above this value inhibition is progressive so that in all animals the acid-forming cells appear to be markedly or completely inhibited by tenth normal hydrochloric acid.

This mechanism appears to be the second bulwark of defense to prevent an excessive rise of the acidity of the gastric *contents.* Should duodenal regurgitation fail to keep the acidity of the contents below a certain value, acid inhibition will then operate to decrease the rate of acid secretion. After the Mann-Williamson operation, and in whole stomach pouches there was evidence that this mechanism operated to decrease the rate of acid secretion as shown by the progressively slower rise in the acidity of the gastric contents toward the end of the experiments (Fig. 1). It is interesting and important to note that when histamine is administered (1 mg. subcutaneously), this mechanism does not operate and marked secretion occurs even when the stomach is filled with 0.170 normal hydrochloric acid. This shows that histamine is qualitatively or quantitatively (or both) different from the normally occurring secretogogues present in food, and it emphasizes the danger of using histamine to study *normal regulatory mechanisms.*

(b) Intestinal acid inhibition. The intestinal phase of acid secretion by the stomach is apparently due to the absorption from the intestine of digestive products which, when they reach the stomach by way of the blood stream, act as secretogogues. It was found that when acid passed into the intestine, inhibition of the intestinal phase of acid secretion occurred, but that the presence of acid in the *stomach did not* inhibit this phase of acid secretion.

The mechanism of acid inhibition is not known, but it is possible that enterogastrone (Ivy) may be concerned in the inhibition of the intestinal phase by acid in the intestine. It seems unlikely that a humoral mechanism is concerned in the inhibition of the intragastric chemical phase by acid in the stomach.

Further studies showed that when the intragastric chemical and intestinal phases coincided, the resulting stimulus to secretion was usually too potent to be inhibited by acid in the stomach and intestine. The degree, then, of acid inhibition depends upon the relative strengths of the *secretory and inhibitory* stimuli.

Acid inhibition is thus seen to act within the stomach to prevent an excessive rise in the acidity of the gastric contents and in the intestine to stop the intestinal phase of acid secretion after the stomach has emptied. Acid inhibition could theoretically control gastric acidity independently of duodenal regurgitation but when both mechanisms are in operation simultaneously it is difficult to determine which plays the more important role. It is possible that the relative importance of the two mechanisms may vary in different persons so that in some individuals duodenal regurgitation may be the primary factor responsible for the control of gastric acidity while in others acid inhibition may be the controlling mechanism. It is also possible that certain types of hyposecretion and hypersecretion may be due to changes in the threshold for acid inhibition in the stomach or intestine.

The effect of acid inhibition on the psychic or cephalic phase of acid secretion was also studied. It was found that this phase is often of such great potency that it is not inhibited by the presence of acid in both the stomach and intestine. Thus the secretory energy of the cephalic phase often approaches that of the simultaneously combined intragastric and intestinal phases and approximates that of histamine stimulation. This is important in showing that the cephalic phase may often be responsible for a degree of hypersecretion or hyperacidity which could not be attained by either of the other two phases alone. The cephalic phase may thus often be correctly termed the "outlaw" among the phases of acid secretion.

IV. THE ROLE OF THE PARS PYLORICA IN ACID SECRETION

Whether or not some stimulus from the pars pylorica serves to augment the secretion of acid by the fundus and thus plays a role in the intragastric chemical phase of acid secretion is a much debated question. One group of clinicians and experimental workers believe that after a Polya or Billroth type of operation, the lowering of gastric acidity can be entirely accounted for by the increase in the amount of duodenal secretions which enter the stomach, while another group believe that the lowering of gastric acidity is more marked than could be accounted for by the presence of duodenal secretions.

We have studied this question using new methods of analysis and calculation which allowed us to determine the amount of duodenal secretions which entered the stomach after Polya and Billroth II operations and found that the decrease in the acidity of the gastric secretions was usually definitely greater than could be accounted for by the diluting and neutralizing effect of regurgitating duodenal secretions.

In some animals however, removal of the pars pylorica failed to produce the usual decrease in the secretion of acid, and our evidence now suggests that this may be due to the fact that in these animals the cephalic or vagal control over acid secretion was unusually marked. In fact, our evidence at the present time suggests that it may be possible to divide animals into two groups, *first*, those in which gastric acidity is greatly influenced by stimuli arising in the pars pylorica and *second*, those in which the acidity is much under the control of cephalic or vagal influences. In the case of the first group, removal of the pars pylorica may produce a marked lowering of acidity while in the second group it may fail to do so, and in these animals a double thoracic vagotomy may have to be performed before the production of acid can be lowered.

It is possible that cases of gastric hypersecretion in man may be similarly grouped, and if this be true, then removal of the distal third of the stomach might be resorted to to control hypersecretion in one group and vagotomy performed to control it in the other group. At present we are subjecting this theory to experimental proof and are attempting to develop methods for recognizing the animals that are to be put into each one of the two groups.

V. WATER ABSORPTION FROM THE GASTRIC CONTENTS

Our evidence indicates that in most normal dogs small amounts of water are constantly being absorbed from the gastric contents but this is hard to show because the quantity of non-acid fluid regurgitating from the duodenum is much in excess of the amount of water absorbed in the stomach. However, when the non-acid fluids from the duodenum are prevented from entering the stomach, as in the case of whole stomach pouches or after the Mann-Williamson operation, the absorption of water may be easily detected; some of the non-acid fluid will disappear as the experiment progresses and as a result the gastric contents will be concentrated and the acidity will rise above the value for pure acid secretion from the parietal cells (Fig. 1).

This phenomenon of absorption and concentration is in some way related to the composition of the normal gastric contents since it does not occur when a tenth normal hydrochloric acid test meal is used. In some dogs water absorption is much more pronounced than in others, and it is in no way related to or dependent upon the degree of dehydration of the animal as a whole. When marked water absorption is associated with a decrease in duodenal regurgitation, a marked degree of hyperacidity may result. It may well be now that there is a clinical type of *hyperacidity* due to an excessive absorption of water from the gastric contents with or without an associated decrease in duodenal regurgitation. This could only be detected by adding phenol red to the fluid of the test meal and determining the amount of total fluid secretions entering the stomach, together with their acidity.

SUMMARY

The physiological control of gastric acidity depends upon the following factors:

1. Strength of the acid secreted.
2. Regurgitation of non-acid secretions from the duodenum.
3. Inhibition of the intragastric chemical phase of

acid secretion due to the presence of acid in the stomach and of the intestinal phase of acid secretion due to the presence of acid in the intestine.

4. The intensity of the stimuli arising in the pars pylorica and the degree to which, in a given animal, they influence the intragastric chemical phase of acid secretion.

5. Vagal or cephalic influences.

6. Absorption of water from the gastric contents.

The relative importance and the interrelations of these factors are briefly discussed.

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Anoxemia Used as a Means of Analyzing the Structure and Functions of the Nervous System of the Bowel*

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SEEING that the several tissues of the body lose their functions at different intervals after the stoppage of the circulation, it occurred to me that this differential death rate might be used as a sort of dissecting needle in physiologic studies, and some eight years ago, when I came to distrust more and more all conclusions based on the assumed actions of drugs, I turned to the use of anoxemia as an aid in unraveling the structure and functions of the nervous system of the bowel.

I first searched the literature for information as to the ways in which the various neurones in the body, as well as the several parts of a neurone, die. A review of this literature has been published elsewhere (5). Suffice it to say here that in mammals', including man, synapses, some of the sensory nerve endings in the central part of the nervous system, and perhaps some ganglion cells, cease functioning within a minute or two after the circulation stops. There is probably a descending gradient of susceptibility from the ganglion cells in the cortex, through the medulla and down to the end of the cord. Consciousness and most reflexes disappear immediately after the stoppage of the heart. After from five to ten minutes the damage done to the nerve cells of the brain becomes irreparable. Some of the nerve fibers and the motor nerve endings in the central nervous system are much hardier, and will function for an hour or two when left in the uncooled animal. Fifteen minutes after stoppage of the circulation in a limb, sensations of touch, pressure, vibration, and position begin to go, and after from thirty to forty-five minutes all that can be felt is warmth and burning pain. With these changes, there is a loss of electric response in the A and B fibers (Clark, Hughes and Gasser).

In the autonomic part of the nervous system, and particularly in the sympathetic division, all parts of the neurone are more resistant to anoxemia than are the corresponding parts of the neurones in the brain and spinal cord. Reflexes persist for from ten to twenty minutes after the stoppage of the circulation, and ganglion cells can be resuscitated after periods of time ranging up to twenty minutes. Stimulation of the vagus nerves continues to slow the heart for about forty minutes, while stimulation of the sympathetic nerves accelerates the beat for a few minutes more. In the intestine, the nervous system, if left in contact with blood, will survive for six hours or more after the stoppage of the circulation; without blood, irreversible changes take place in about three and a half hours.

THE WAY IN WHICH THE INTESTINE OF THE RABBIT LOSES ITS FUNCTIONS AFTER THE DEATH OF THE ANIMAL OR THE STOPPAGE OF THE CIRCULATION.*

PERISTALTIC RUSH

I have long known that in the dying rabbit, the first function of the bowel to be lost is that of peristaltic rush; it disappears immediately. In twenty years I have seen only a very few examples of what looked like a normal rush in the intact bowel left in a dead animal with the abdomen open in a bath of warm aërated saline solution.

At first glance it would seem that any function that disappears so promptly after the stoppage of the circulation must be dependent on a synapse as sensitive as are those in the higher parts of the central nervous system. In favor of this view is the fact that the injection into the animals of a little nicotine usually puts an end to the rushes. But against the view are a number of observations. One is that the synapses in the sympathetic division of the nervous system appear usually to retain their function for from ten to twenty minutes after the stoppage of the circulation, and from Cannon and Burket's experience, one would expect the synapses in Auerbach's plexus to be even more resistant than are those elsewhere in the abdomen. Perhaps confirmatory of this view is my observation (4, 8, 9) that the synapses that presumably exist between the vagus nerves and the neurones in Auerbach's plexus retain their function for from ten to twenty-seven minutes after the death of the animal. The evidence in favor of the view that such synapses exist has been summed up elsewhere (7).

It seemed probable, then, that the immediate stoppage of rush waves which is usually observed when

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*In the experiments herein described the rabbits were anesthetized with urethane. The distal part of the spinal cord was pithed and the abdomen was opened under a bath of warm Locke's solution. The technic used in starting and recording rushes has been described elsewhere (Alvarez) (6).

the heart ceases beating is due to inhibition, and this view was strengthened by two observations. One was that with the stoppage of the rushes, there was, at times, a stoppage also of the rhythmic contractions of the muscle. This took place even when the saline bath was aërated. That it was due to inhibition was indicated by the fact that the rhythmic movements promptly reappeared when the bowel was cut away from the mesentery. The other observation was that if, instead of sacrificing the animal, I stopped the circulation in the bowel by clamping the abdominal aorta or the superior mesenteric artery, the rush waves often stopped for a few minutes, only to reappear, much as the rhythmic contractions did. The rushes could be elicited then for a few minutes until, perhaps, with loss of function in some synapse, they stopped, never to reappear.

When the intestine was left attached to the mesentery of the dead animal the rushes never reappeared, perhaps because by the time the inhibition had worn off, irreversible changes had taken place in the synapses. This inhibiting effect may come by way of the nervous system or it may come through the blood from other parts of the dying body. The latter theory is probable because the inhibition was often absent when the stoppage of the circulation was effected by clamping the mesenteric vessels, and it could then be produced sometimes by removing the clamp and letting the blood flow in again. It is interesting to note here that Carnot and Glénard (24, 25) found that a segment of bowel would survive better if they washed out the blood vessels. Interesting, also, is Nolf's (41) conclusion that, in the chicken, the stoppage of the movements of the gizzard which follows asphyxia is due to stimulation of a nervous center which produces inhibition. Somewhat similar observations on the behavior of the arrectores pilorum muscles of dying animals were puzzled over years ago by Langley (37, 38).

That some form of inhibition of the intestine is removed after the death of the animal was suggested by a number of observations. Thus, I found that the tonic effect of electric stimulation of the vagus nerves on the muscular contractions of the bowel was easier to demonstrate immediately after death than it was in the living animal. Similarly, the short distance conduction of an electrically produced disturbance was more easily demonstrated in excised than in intact bowel. Other investigators have made similar observations.

Difficulties in differentiating normal and abnormal rush waves: Unfortunately, as I (6) have pointed out elsewhere, definite conclusions as to the length of the interval between the death of an animal and the cessation of rushes are hard to draw because so much depends on the experimenter's opinion as to the normality or abnormality of each wave seen. The problem would be much simpler if inspection of the graphic records could decide the matter, but often this does not help much. The difficulty lies not only in the defects in the methods of recording, but also in the fact that some of the rushes observed in apparently healthy bowel are atypical or perhaps as abnormal as those seen in nicotinized or dying bowel. Usually the dying or nicotinized bowel empties itself poorly after a rush, but bowel that appears to be normal will often do the same thing, and bowel that has long been anoxemic may seem to empty perfectly (Fig. 1). Sometimes the main abnormality of a questionable rush is its fast rate, or its tendency to combine the characteristics of both a "systole" and a rush.

I regret that for some time I used recording devices, attached to the longitudinal and circular muscle, which did not facilitate the differentiation of normal and atypical rushes, or rushes mediated by some mechanism other than the normal nervous one. Eventually I devised a satisfactory "distention recorder" described elsewhere (6).

The study of peristaltic rush is made particularly difficult by the fact that there appear to be a number of ways in which the intestinal contents can be made to travel through the bowel. Actually, a column of fluid rushing down the bowel with good momentum can be made to pass through 100 cm. or more of dead bowel or even through a length of glass or rubber tubing. When some of this fluid reaches normal bowel at the further end of the inert segment, it commonly starts a new wave which proceeds normally on toward the ileocecal sphincter. Other ways in which the rushes can travel will be described later in this paper.

Rushes seen after clamping the abdominal aorta: In a series of sixteen experiments, the aorta of the rabbit was closed just below the diaphragm, usually with the help of a snare made with a metal tube and a piece of tape. In every case the bowel was rendered pulseless and either blanched or scanotic. In a few of the experiments I observed the immediate inhibition of rushes which is so characteristic after the death of the animal. Usually, after a few minutes, they could again be elicited. In animals which showed but few rush waves before the clamp was applied, it was hard to start any after the circulation was stopped, while in robust animals with a very active bowel to begin with, an hour or two of anoxemia sometimes did not do much harm. These differences in individual rabbits added greatly to the difficulties of interpreting the results of experiments.

Some rushes started spontaneously, but most of them were produced by squirting fluid into the duodenum according to the technic described elsewhere (6).

So far as my assistant and I could tell from the appearance of the rushes, they were normal for from twenty to thirty-five minutes after the stoppage of the circulation. This interval agrees fairly well with that representing the usual survival time of synapses in the sympathetic nervous system and also of those synapses which are believed to connect the ends of the vagus nerves with the neurones of the myenteric plexus. After half an hour of anoxemia, the graphic records of rushes often looked fairly normal, but the waves themselves commonly did not look right to the experienced observer. Some seemed to go too slowly, others too fast, others too weakly, and others seemed to be mixtures of systoles and rushes, usually running caudad but sometimes orad. Actually the records often indicated that a series of short waves had arisen simultaneously in several parts of the bowel and had traveled caudad or orad.

Very puzzling was the fact that in one rabbit with the aorta clamped, after good rushes had run for thirty minutes, questionable ones continued to appear for three hours or longer; in one animal, what looked like a normal rush was recorded three hours and thirteen minutes after the bowel had first been rendered pulseless and cyanotic. In another animal,

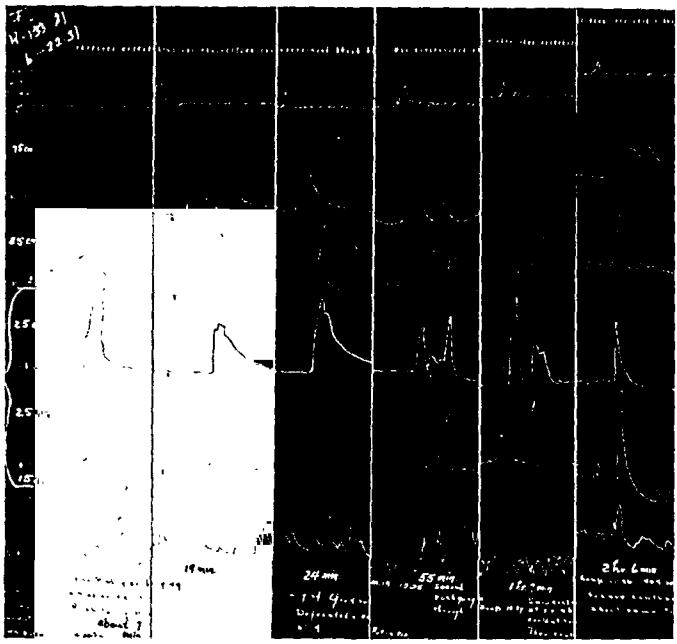


Fig. 1. Showing the change from a wave to a systole produced by anoxemia: *a*, record of a normal rush coming seven minutes after the segment indicated by the brace had been cut away from its mesentery; *b*, twelve minutes later a wave progressed normally until it reached the anoxemic segment and there it traveled rapidly; *c*, five minutes later a rush went through the anoxemic segment even more rapidly; *d*, thirty-one minutes later the anoxemic segment contracted as a unit the moment a rush reached its oral end, and contracted systolically again thirty-two seconds later; *e*, twelve minutes later, or sixty-seven minutes after the segment lost its blood supply, it failed to conduct a rush; instead, the caudal end contracted at almost the moment when the rush left the duodenum 160 cm. away, and originated a wave which ran orad until it met the descending rush, and *f*, after two hours and six minutes of anoxemia the contraction of the anoxemic segment was typically systolic; in the bowel orad and caudad to the abnormal segment rushes still traveled normally.

after the circulation of the bowel had been shut off for about an hour, first by clamping the aorta and later by cutting through the root of the mesentery, an apparently normal rush was seen. It is hard to know what to think about these observations. Either synapses survived unusually long because some trickle of blood continued to come in through collateral channels or else I was mistaken in my opinion as to the normality of the rushes, or perhaps synapses are not so important in the mechanism of peristaltic rush as I think they are. Good examples of the changes in the appearance of rushes which come with anoxemia are to be seen in Figures 1 and 2.

In eleven animals the clamp on the blood vessels was removed after varying intervals of time to see if the rushes would become normal again. In no instance did they seem quite normal when the anoxemia had lasted over half an hour. One must not conclude from this that changes in the nerves are irreversible after this length of time because experiments of another type showed that they are reversible. The experiments to which I now refer resembled those of Cannon and Burket in which clamps were applied under aseptic conditions so as to stop for several hours the circulation of the bowel. Later these clamps were removed, and the animal was allowed to recover. In one such experiment, to be described later in more detail, rushes which appeared to be normal were seen traversing a long segment of bowel which, three weeks before, had been kept pulseless and purple for twelve and a half hours!

Rushes seen after clamping the superior mesenteric artery: In nine animals, the superior mesenteric artery was clamped, and the results obtained were very much like those seen after clamping the abdominal aorta. If there were good rushes before the artery was clamped these generally continued for about thirty minutes, and after that they were atypical (Fig. 2).

Rushes after clamping the mesenteric vessels to a segment of bowel: In thirteen animals the mesenteric arteries supplying a segment of jejunum or ileum approximately 140 cm. in length were clamped for varying periods of time. In every experiment most of the segment became cyanotic, but some blood continued to trickle into the ends adjoining the normal bowel.

Again, in the more healthy animals in which there were good peristaltic rushes before the vessels were clamped, waves continued to pass normally through the cyanotic segment for from eight to thirty-seven minutes. Then there usually came a change; the bowel often became beady as it does after it has been

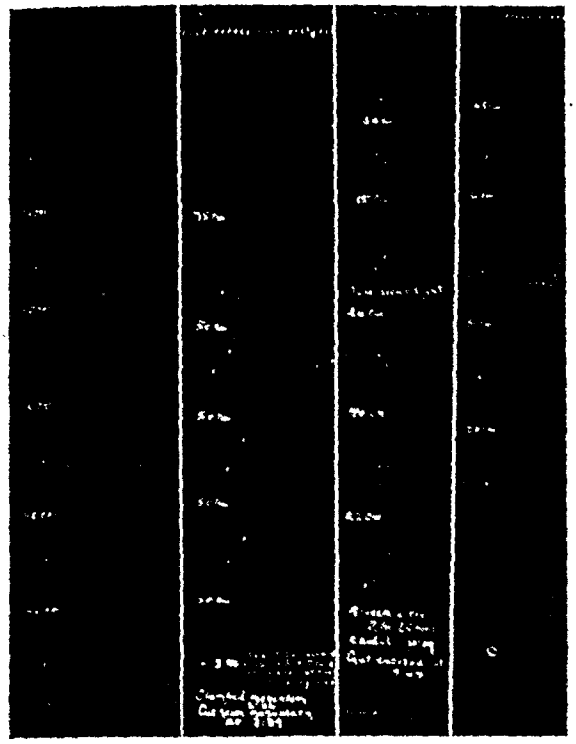


Fig. 2. *a*, a slow rush wave; *b*, a fast traveling disturbance in the same bowel forty-six minutes after the mesenteric vessels were clamped and three minutes after the bowel was cut away from the mesentery; to the observer the disturbance looked like a normal rush in the first 125 cm. of bowel, but what happened caudad to this point was not so clear, the record showing that the contraction was systolic in type and that it began as the wave left the duodenum; *c*, 145 minutes after the bowel had been separated from the mesentery a disturbance was made to travel orad the length of the bowel; that this was not due purely to an advancing column of fluid is shown by the fact that about midway the lumen of the bowel was closed with a ring of tape; in addition to the traveling wave, there was an immediate response of the bowel 92 cm. orad to the point stimulated; and *d*, rarely seen wave of inhibition running down the bowel.

poisoned by nicotine, and the rushes then became shallow and discontinuous. Such atypical rushes often continued for a long time. In one animal, they were still going through with some signs of a following wave of contraction four hours after stoppage of the circulation. In this particular experiment, the rhythmic contractions had ceased, but the long-distance nervous paths, to be described later, were still functioning well, as shown by the fact that some segments of the injured bowel were "anticipating" the arrival of the rush waves with an increase in tonus and activity.

After the first half hour of anoxemia, rushes entering the upper end of the cyanotic segment sometimes faded out and failed to reach the distal end. Whenever they did reach it, they always went on caudad with a normal appearance in the normal bowel. So long as the rushes could get through the cyanotic segment they usually traveled there with a normal rate. Sometimes they went through abnormally fast.

The removal of the clamp and the restoration of the circulation after an interval of from twenty to thirty minutes resulted after a time in the return of perfectly normal rushes.

In some cases the root of the mesentery was cut between clamps, and in one such case records of rushes looked normal one hour later. They looked fairly normal to the observer, but they decelerated instead of accelerating in speed, as they should normally have done.

At times, the observers could see a change in the character of the rushes after the first thirty minutes, but examination of the graphic records did not help in determining what was wrong with them. In one experiment the records of the rushes looked normal for an hour and forty-seven minutes after the tying of the arteries. When the rushes could no longer get through an anoxemic segment they seemed to enter it and go normally for a distance of perhaps 20 cm. They could do this perhaps because near the end of the handicapped segment there was still some inflow of blood.

Rushes seen after cutting segments of the bowel away from the mesentery: In ten rabbits segments of bowel were cut away from the mesentery after ligation of the vessels supplying the region. The blood remaining in the bowel was forced out by tonic contraction of the blood vessels, so that the wall became blanched and often beady. When the segment was less than 65 cm. long, rush waves continued to run through it as if nothing had happened; when it was from 65 to 170 cm. long, the waves commonly got through but they were abnormal in one way or another. Sometimes when they looked normal to the observer they appeared to be abnormal on the record (Figs. 1 and 2).

In a number of experiments most of the small bowel was cut away from the mesentery, leaving only the blood supply of the duodenum intact. The plan was to start rushes in this first part of the bowel and see how far they would go. In most of the rabbits so prepared rushes could not be started, but in one rabbit some very interesting observations were made: Eight minutes after nearly all of the jejunum and ileum (235 cm.) had been separated from its mesentery, an apparently normal rush went through and another followed two minutes later. After this there were no more.

Rushes seen after removing the whole small bowel from the body: In a series of eighteen experiments the whole small bowel was removed quickly and placed in a tank of warm aërated Locke's solution. Recording devices were attached at intervals along this bowel, as in the experiments with intact animals. When fluid was squirted into the oral end of such excised bowel, there seldom appeared anything that could be mistaken for a normal rush wave, at least during the first hour or two. During this interval the fluid injected usually worked its way slowly toward the caudal end, leaving the bowel constantly distended. When contractions appeared here and there they usually progressed for some distance caudad, but there was no coördinated rush traveling a long distance.

Rarely, there seemed to be exceptions to this rule, and what looked like normal rushes would appear, usually in the first few minutes after the death of the animal. Once this may have been because the mesenteric artery was clamped as the animal was dying, thus cutting off the access of inhibiting substances to the bowel.

One day Dr. Berkson and Mrs. Bennett, who were working with me, saw several spontaneous and apparently normal rushes traversing about 50 cm. of bowel which had been out of the animal and in oxygenated Locke's solution for about one hour. The contractions of the muscle were powerful and the waves seemed to advance continuously. In the case of one such wave which I watched closely the successive segments of bowel traversed by the disturbance emptied themselves promptly and efficiently, which is a good sign of normality. Evidences of normality could be seen also in the graphic records made of this rush which appeared nearly three hours after the death of the animal. In another instance the records made nearly three hours after excision of the bowel showed what looked like good rushes with signs of "anticipation," or an increase in the tonus and activity of the bowel far out ahead of the crest of the wave.

In two other experiments waves were still traveling caudad six and a half hours after the gut had been removed from the body. Some of these were almost normal in appearance, not only to the observer but to the analyzer of the graphic records.

Difficulties in the appraisal of these late appearing rushes were multiplied because of the fact that after from one to three hours of anoxemia, long-distance conduction usually improved so markedly that there appeared many systoles (Fig. 5) or mixtures of systoles and short rushes (Fig. 3) which often seemed to the observer to be fast rushes. Perhaps the greatest uncertainty in all this work arose in the fact that often, long after the rush waves had apparently stopped or had become decidedly abnormal, along would come one in which no fault could be seen.

This occasional long persistence of what looked like rushes in excised bowel was hard to reconcile with the observations made with the anoxemic bowel left attached to the mesentery. A few things seem certain from the experiments recorded in Figs. 3, 4 and 5: one is that some of the nervous pathways for the long-distance type of rapid conduction must be in the bowel itself; another is that these conduct in either direction, and another is that they are remarkably immune to anoxemia. It seems probable also that the more sensitive nervous mechanism which presides over normal rushes resides in the bowel; the polarity which causes waves to travel more easily in one direction is certainly resident in the wall of the bowel.

The importance of the advancing column of fluid: As I have already said, yet another difficulty in the way of saying when normal rushes stop is to be found in the fact that there are a number of ways in which rushes can be kept going. In another paper I hope to show in more detail how the mere advance of a column of fluid through the bowel may serve to maintain or keep going what looks like a rush. The importance of this mechanism is shown by the fact that in bowel handicapped by anoxemia, rushes seldom got past a point where the lumen had been occluded by a ring of tape drawn just tight enough to prevent the passage of the intestinal contents. In normal bowel, such obstructions seldom had much effect because the wave could travel through the muscle to pick up a new column of fluid on the other side of the ring (2).

The importance of the advancing column can be seen also from the following experiments: In the first one, excised bowel was cut across and the lumen was

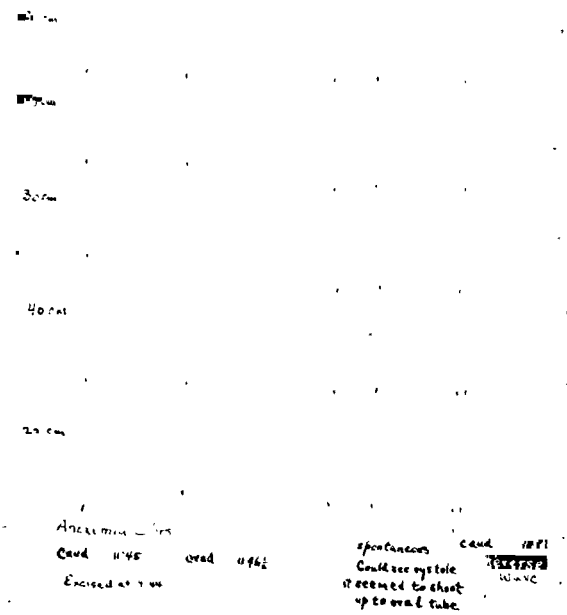


Fig. 3. Types of activity in excised whole bowel, kept in warm oxygenated Locke's solution for about two hours: The first stimulus, applied at the caudal end, appears to have spread orad as a faint ripple for 62 cm. The second stimulus, applied at the oral end, produced two disturbances, one of which shot almost instantly 75 cm. to the fourth recording segment from the top; the other, a wave, spread rapidly to the caudal end of the bowel. Next came two spontaneous disturbances, the first of which apparently originated at the caudal end and shot almost instantly 107 cm. orad. To the observer it looked like a rapid wave. The next disturbance appears to have begun in the middle and spread both ways. Then a stimulus was applied to the caudal end, producing what seemed to be a wave running orad for at least 107 cm.

restored with a short segment of glass tubing, any rushes that appeared then ran on without hesitation, in spite of the fact that there could have been no preparation of the segments caudad to the cut. In the second experiment, the bowel, attached to its mesentery, was cut across and the end was left open so that when a rush arrived the fluid ran out into the bath. Under these circumstances a wave never went on down the distal part of the bowel. In the third experiment the wall of the bowel was crushed with a hemostat in eight places, distant about 5 cm. one from the other. When rushes continued to go normally through this series of segments held together only by narrow bands of dead tissue, it was apparent again that the moving column of fluid within the lumen must be an important factor in keeping the wave going.

Important as this moving column of fluid is, however, it apparently must be assisted by the gradient or the "polarity" of the gut or whatever it is that causes the waves to move caudad in every short length of intestinal muscle. Were it not for this it should be

as easy to make waves run orad as it is to make them go caudad, simply by injecting fluid into the caudal end of the bowel, intact or excised. Actually, on attempting this, in both normal and anoxemic bowel, I found that with one squirt of fluid into the ileum, a wave could be forced orad for only about 80 cm.; there it usually faded out, and then the fluid was driven back caudad. Two mechanisms seemed to be working against the success of the experiment; one, the "long-distance conduction" which caused contractions to appear some distance ahead of the reverse waves, and the other, the gradient which caused each one of these contractions to spread caudad as a wave (Fig. 3).

Poor emptying of the anoxemic bowel: One important point to be noted about all of the atypical rush waves in anoxemic or nicotinized bowel is that the injured muscle usually did not contract well so as to clear the liquid contents out of successive segments (see Fig. 1, Alvarez) (7). Since there is much evidence to indicate that smooth muscle does not lose its faculty of contraction until anoxemia has lasted for several hours, one must suspect that the poor emptying of the abnormal gut is due to some failure either in the nervous pathways which transmit stimuli from the mucous membrane to the overlying muscle bundles, or else to interruption in the short conducting paths which cause many muscle bundles to contract together in a coördinated way. Actually, a number of investigators have found that cocainization of the mucous membrane of the bowel tends to disorganize peristalsis in the treated segment.

Reverse peristalsis after anoxemia: In several instances the shutting off of the circulation from a long segment of bowel brought with it a tendency to reverse peristalsis, but it seemed clear that the gradient in the bowel had not been much altered because contraction rings appearing here and there usually traveled caudad. Because some of the gradients tend to be reversed in pregnant animals (Alvarez and Hosoi) (11), I tried adding the reversing effect of anoxemia to that of pregnancy, but without much success in reversing the direction of rushes. They would not run orad very far even when fluid was squirted into the lower end of the ileum.

Peculiar, fast rushes: In some animals with an anoxemic bowel I saw a type of disturbance new to me. This appeared to be a very fast rush with a rate of travel varying from 30 to 65 cm. a second. Usually in the normal rabbit the rate varies from 3.5 to 6.5 cm. a second, but occasionally in the ileum a rush will traverse 25 cm. in a second.

SURVIVAL OF NERVES AND NERVE ENDINGS

After having obtained some idea of the survival time of what I assumed to be synapses in Auerbach's plexus, the next problem was to see how long the nerve fibers and their motor endings would function after the death of an animal. Only a study of action currents would enable one to determine the survival time of a nerve fiber if this time should happen to be longer than that of the motor ending. Hence now when I say "nerve" I mean the fiber together with that series of mechanisms which carries the nervous impulse over into a contraction of the muscle (Rosenblueth and associates) (46, 47).

Years ago Elliott concluded that the myoneural junction depends for continuance of life on the nucleoplasm of the muscle cell, not of the nerve cell; and actually, in the bowel, I have found the nerve endings to be very hardy. Time and again, what I call "long-distance effects" appeared in segments so poisoned by anoxemia that they gave no response to direct faradic stimulation. These endings and the fibers were immune also to doses of nicotine large enough to kill the animal, and they were immune to atropine.

Conduction over short distances: The first form of nervous conduction studied was that which is brought about through stimulation of the bowel with an interrupted electric current. Hosoi and I (12) found that in rabbits the constant current, or a single shock or a pinch, produced a contraction which did not spread along the bowel. The disturbance produced by an interrupted stimulus spread at most about 15 cm. orad and 20 cm. caudad, and considerable evidence was gathered to show that this conduction took place along short nervous pathways. These pathways did not seem to be injured by nicotine. According to Fleisch a similar type of conduction in the guinea-pig was blocked by dilute solutions of nicotine. Fleisch and Wyss blocked it also with atropine and cocaine. Raiford and Mulinos (44, 45), using denervated exteriorized segments of colon in dogs, were able to block conduction between the mucosa and the overlying muscle with atropine, and they obtained blockage also by cocainizing the mucosa.

Immediately after the bowel was excised and put into warm Locke's solution, some form of inhibition disappeared and short-distance conduction could be demonstrated more easily than when the bowel was attached to the mesentery in the living animal. This was observed also by Fleisch and Wyss, using guinea-pig bowel.

When I kept the bowel in warm aërated Locke's solution this short-distance conduction disappeared usually after about 100 minutes, but sometimes it lasted for from three to five hours (4). This interval could be doubled by filling the bowel with oxygen. In one such experiment, conduction was unimpaired after six and a half hours, when the observers left the laboratory. Such survival times are compatible with the idea that this type of conduction is mediated by nerve fibers.

Puzzles still remain, however, because from what is now known of the great dependence of smooth muscle on nerves for all but the slowest type of transmission of a stimulus, it would seem that so long as segments of bowel a few centimeters long are contracting, nerves must be at work. If this is true, then there must be two types of nerves conducting over short distances: one that loses function after some 100 minutes of anoxemia, and the other, one that survives for hours or perhaps for as long as the muscle survives. In support of this view may be the fact that degenerative section of the splanchnic nerves which commonly seemed to destroy the conducting paths with a survival time of 100 minutes did not prevent short segments of bowel from contracting in a coördinated way.

That there can be complete failure of conduction between muscle fibers, with such incoördination of activity that the many contractions and relaxations cancel out and have no effect on the length of even a short segment of bowel, was shown by me years ago while I was studying young alligators. Puzzled because with the usual heart levers I could not detect the slightest sign of activity in segments 2 or 3 cm.

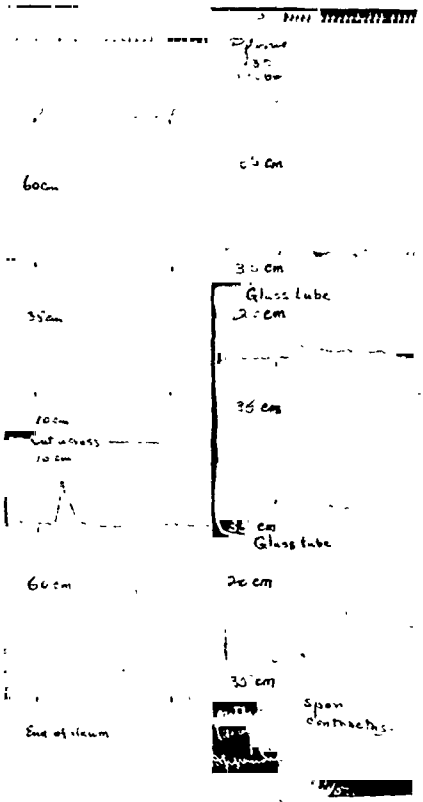


Fig. 4. Showing that some of the long nerve tracts are in the mesentery; *a*, in spite of the fact that the bowel was cut across, the ileum was inhibited when the duodenum was stimulated and *b*, similarly, with the bowel cut across in two places, a rush in the duodenum promptly affected the lower ileum. The record shows that the stimulus was not transmitted by the column of fluid because this did not get through the separated segment 90 cm. in length.

long, I looked with a microscope and found that the trouble was that every muscle fiber was busily contracting and relaxing, but each was out of step with its neighbor. Probably in these animals, as in the elasmobranch fishes, and to some extent in mammals, the power to conduct appears from time to time suddenly and for no known reason in smaller or larger portions of the enteric nervous system. One of the greatest needs today in the field of intestinal physiology is light on the nature of the mechanism which at intervals hooks this conducting system together and makes it work.

In twenty-seven rabbits studied with the technic used by Hosoi and me (10) for stimulating the bowel, the first function of the bowel to disappear was usually conduction orad of the disturbance produced by faradic stimulation. Conduction caudad lasted longer, perhaps because it is easier for impulses to go in that direction with the gradient. The local response to the faradic current disappeared next; then the rhythmic contractions, and finally the ability to respond to a slowly interrupted galvanic current.

If Nolf's (42) idea of a chain of neurones along the bowel was applicable in the case of the rabbit, one might expect to find, after a half hour of anoxemia had injured the synapses, a sudden, step-like shortening of the distance over which conduction could take place. Actually, in scores of experiments, Hosoi and I failed to observe any such change, and we failed to see it also after applying nicotine. This drug impaired the responses to stimulation, but we could not see that conduction failed segmentally as Nolf found it to do in the chicken. Also, much against Nolf's idea of a chain of conducting neurones in the myenteric plexus is my observation that in the rabbit, degenerative section of the splanchnic nerves almost wiped out what I call "short-distance conduction" throughout the small bowel, and degenerative section of the vagus nerves often shortened the distance over which such conduction could be demonstrated in the lower part of the small bowel (16). These observations indicated that, in the rabbit, much of this type of conduction is effected by fibers belonging to the *extrinsic* nervous system; Nolf believed it to be effected by *intrinsic* nerves. Fig. 12 in an article by Borchardt showed that conduction caudad was good in a denervated segment of bowel. Borchardt found also that denervation of the bowel did not interfere with the transmission of stimuli between the mucosa and the overlying muscle. According to Langley and Magnus, degenerative section of the mesenteric nerves had little effect on conduction in the bowel.

I have records showing what I call "long-distance conduction" in rabbits with both vagus nerves cut and degenerated, and I have others showing it in the bowel from animals with both vagus and splanchnic nerves cut on the day of the experiment. Unfortunately, I cannot now find any records throwing light on this point in animals with the splanchnic nerves cut and degenerated.

Few of my observations seem, then, to fit well into Nolf's attractive theory of a chain of neurones down the bowel. Perhaps this theory applies only in the case of the chicken. It is conceivable, however, that in the bowel of the rabbit, neurones about 35 cm. long, instead of being arranged like the links of a chain, overlap like the fibers in a rope. It may be, also, that there is no transmission across synapses except when a rush gets started. Against Nolf's idea that valve-like synapses between the neurones in the chain prevent reverse peristalsis is the fact that reverse waves of some kind can often be seen in the rabbit and cat. Their guiding mechanism may perhaps be very different from that of the normal caudad-directed waves.

Rapid conduction over long distances: Years ago I reported the fact that, almost coincident with the start of a rush down the duodenum, there were changes in the level and appearance of records being made of the activities of the jejunum and ileum (15). There was some increase in the tonus and activity of a segment of bowel here and there, or one rhythmic contraction was either lessened or increased in amplitude, or one or two such contractions were blocked, or the interval between two contractions was shortened or lengthened. Similarly, defecation sometimes paralyzed the whole small bowel for a few seconds.

It seemed obvious that the stimuli which produced these effects so promptly must be transmitted through nerves. Occasionally, these long-distance effects, as I call them, can be elicited by a faradic stimulus, but the best way in which to demonstrate them is to start a rush wave in the upper bowel. Interestingly, these effects commonly tend to skip one segment of bowel

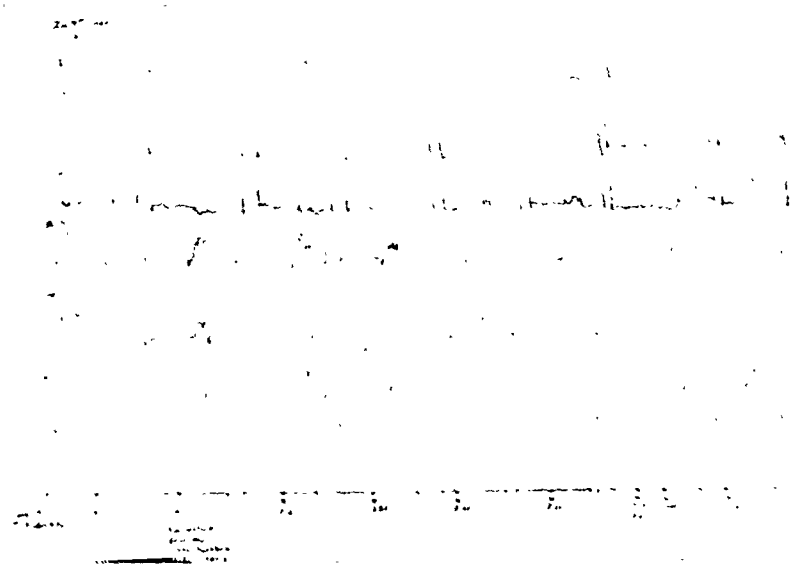


Fig. 5. A series of systoles in 130 cm. of excised bowel lying in warm oxygenated Locke's solution. Each contraction was produced by the injection of water at the oral end. The animal was sacrificed at 9:51 a. m. and the experiments here recorded were performed between 2:40 and 4:25 p. m., or from four hours and forty-nine minutes to six hours and thirty-four minutes after the bowel had lost its circulation.

to affect others near by. Possibly, one region is ready and another is not. In favor of this view is the fact that the presence of active rhythmic contractions in a segment seems at times to block the reception there of long-distance stimuli.

When I began to study the anoxemic bowel I soon noticed that the long-distance effects came out strikingly after the bowel had been without its circulation for a few hours. Then, after peristaltic rushes, short-distance conduction, and perhaps even the rhythmic contractions had failed, the long-distance conduction came to the fore, and the hardy nerves involved seemed to take over the direction of activities in the gut. It was interesting to note that the same thing happened in many of my animals when the nervous mechanism underlying peristaltic rush was put out of action by nicotine (7).

The most striking manifestation of the long-distance type of conduction I have called a "systole" because of the almost simultaneous contraction of the muscle in many parts of the small bowel. Often these systoles are associated with a series of small rushes (Fig. 3).

The fact that the mechanism that produces these manifestations is so highly resistant to anoxemia and to nicotine suggests that it consists of long nervous paths unbroken by synapses. That these paths must be present in both bowel and mesentery was shown by the persistence of long-distance effects in both excised bowel (Figs. 3 and 5) and normal bowel cut across in one or more places (Fig. 4). Fig. 3 shows that these nerves conduct in either direction, orad or caudad.

Function in these long pathways tended to fail after from five to seven hours of anoxemia, but my impression was that in healthy and active animals, or in intestine filled with oxygen, it could be maintained much longer. Thus, on several occasions, powerful systoles were being observed in the bowel some six or seven hours after the death of the animal when, because of the closing of the laboratory, the experiment was brought to a close.

Just as with short-distance conduction, so also with the long-distance type, there was considerable evidence to indicate that impulses would continue to travel caudad for some time after they had ceased going orad.

Rapid conduction by means of "water waves": I have reasons for believing that, at times, when a stretch of bowel is full of fluid, a type of long-distance conduction is effected by a stimulus transmitted through the fluid to receptors in the mucosa or the muscle. Occasionally, long-distance effects seemed harder to demonstrate when, in order to eliminate the possibility of transmission through fluid, I closed the lumen of the bowel here and there with a snugly applied ring of tape. That usually the transmission was through nerves and nerves alone was shown by experiments such as that recorded in Fig. 4. It was shown also by experiments in which the bowel was stimulated electrically or by suddenly distending a balloon in the duodenum.

LIGHT THROWN BY ANOXEMIA ON THE ACTIVITIES OF THE INTESTINAL MUSCLE

There are reasons for believing that if the excised bowel were to be kept in a stream of warm oxygenated Locke's solution, perhaps with dextrose added, the rhythmic contractions would last for days, to be stopped only by the advent of bacterial and autolytic decomposition. In some of my experiments in which the solution was changed every hour or two the contractions stopped in from five to six hours, but on several occasions they were going well after eight hours when the observers had to leave the laboratory.

In some experiments in which enough boric acid was added to the Locke's solution to make a 0.05 per

cent solution, the rhythmic contractions lasted longer than usual.

Usually, after the death of the animal or excision of the bowel, the rate of rhythmic contraction was slowed. Because approximately the same amount of slowing was usually produced by cutting both the vagus and the splanchnic nerves and allowing them to degenerate, and because after such denervation death of the animal or excision of the bowel did not cause much more lowering in the rate, it seemed that the extrinsic nerves of the bowel must contribute something to speed up the rate of the rhythmic contractions (16).

Curiously, I did not see much slowing of the rate immediately after the extrinsic nerves were cut. The big change came after degeneration of these nerves, and particularly after degeneration of the splanchnic nerves. Curiously, also, the slowing did not appear in all animals operated on. Castleton saw slowing when in dogs he denervated a loop of bowel which had previously been transplanted out under the skin.

Practically all of the available evidence now indicates that the rhythmic contractions of the bowel can keep going in the absence of any nervous impulse, but that in the normal intact animal the nerves play some part in the pace-making process just as they do in the case of the potentially automatic heart of Limulus (Heinbecker and Bishop). This nervous help seems to be needed most in the distal end of the ileum where Auerbach's plexus thins out (17). It is curious that this aid should come from the extrinsic nerves of the bowel, but perhaps it comes from some of those many fibers in Auerbach's plexus which disappear after degenerative section of these nerves. It is curious also that on warming to 38° C. excised bowel that has been in the icebox for twenty-four hours, the rate of rhythmic contraction will sometimes return almost to normal (1). This is hard to explain.

Much light on the nature of the relationship between the nerves and the rhythmic contractions of the bowel will probably come some day from further investigation of the fact that good "action currents" can be obtained from temporarily quiet stomach or bowel (13), or the fact that while epinephrine and atropine stop the contractions, they leave the electrogram unchanged (Alvarez and Mahoney (14), Berkson (18), and Castleton); or the fact that while nicotine and curare wipe out the electrographic changes, they leave the contractions more powerful than before (Berkson (19, 20), Puestow). Curiously, large doses of cocaine and ergotamine had no effect on either the myogram or the electrogram.

The recent work of Heinbecker indicates now that, in the cardiac nerve cord of Limulus, the comparatively slow potential alteration, the rate of which corresponds to that of the heart, arises in the large unipolar ganglion cells. The future alone will tell if similar conditions are present in Auerbach's plexus, and if the currents derivable from the active bowel are produced, as it now appears, in the ganglion cells rather than in the muscle.

After studying the problem off and on for years I still do not understand why the rhythmic contractions sometimes stop within a few minutes after the death of the animal and at other times go on unchanged. This stoppage was observed sometimes after clamping the mesenteric vessels. When this happened it could not be due to anoxemia because, when the bowel is cut away from the mesentery, it goes on contracting rhythmically for hours. In some of the experiments in which the aorta was clamped for a time the stoppage came immediately after the clamp was removed, indicating that some inhibiting substance arrived with the returning blood. A sudden slowing when the circulation failed in the dying animal was seen even in animals sacrificed by an overdose of nicotine. In them the rate had already been slowed by the drug.

Not infrequently irritability and conduction (over short distances) disappeared at the beginning of a period of anoxemia, only to reappear later when the rhythmic contractions stopped. This sort of thing added greatly to the difficulties of drawing conclusions, and necessitated much repetition of experiments.

THE REMARKABLE ABILITY OF THE NERVES OF THE BOWEL TO RECOVER AFTER LONG PERIODS OF ANOXEMIA

Nolf (42) concluded from experiments with nicotine that in the bowel of the chicken there is a second stage of neurones in the myenteric plexus, situated between the longitudinal nerve chain and the muscle fibers. I was particularly anxious to identify and study these second-stage neurones. Granted that they exist, I hoped to find some way of putting them out of action, because if they could be destroyed in any short segment of bowel, there are reasons for believing that, like the muscles in some lowly forms of life which contract into a hard knot whey they are cut off from their ganglion, the muscle in the bowel would contract spastically and permanently (3). Such a disturbance could easily account for some of the spastic contraction rings which cause obstruction, particularly in the bowel of children. I did much work with the hope of finding some neurotoxin or some amount of anoxemic injury that would destroy this hypothetic second-stage neurone without injuring the muscle, but I did not have any success. If such neurones exist in the rabbit they must be about as hardy as is the muscle.

In one series of experiments, resembling those of Mall, Cannon and Burket, and Scandola, Mrs. Bennett operated on rabbits under ether and clamped, for from four to twelve hours, the arteries supplying a segment of bowel. The circulation was then restored, the abdomen closed, and the animal allowed to recover. After from two to three weeks it was again anesthetized, and the bowel was studied in the tank with my usual technic. It was then found that peristaltic rushes went through the previously anoxemic segment without any demonstrable abnormality. These experiments showed, perhaps even more conclusively than did those of previous experimenters, that the intrinsic nervous system of the bowel is about as resistant to anoxemia as is the muscle in which it is embedded. In this way it seems to differ from nervous tissue everywhere else in the body.

There is one possibility, however, and this is that nerve fibers everywhere survive as long as does muscle; what looks like a failure of conduction in the nerve fiber may be only a failure of the muscle to respond to the exciting substance that is formed at the ends of the nerves. Against this assumption is the finding that, with anoxemia, two of the components of the electric response of a nerve to stimulation disappear (Clark, Hughes and Gasser). It would be in-

teresting to see if such changes could be observed in the case of the intestinal nerves.

Berkson (21) studied anoxemic bowel at various intervals up to three days to see if at any time while the muscle was still contracting well the rhythmic currents would disappear as they did under the influence of nicotine, but he could not get any clear-cut results. The impression was that the currents became irregular and weak as the contractions became irregular and weak, which perhaps supports the evidence suggesting that ganglion cells in the bowel are about as hardy as is the muscle. Dr. Kernohan, the neuropathologist, examined for me sections of the myenteric plexus from bowel that, three weeks before, had survived several hours of anoxemia, and found the ganglion cells so edematous and abnormal that he doubted if they could be functioning. Nevertheless the motor functions of the bowel seemed to be normal.

COMMENT

The most interesting discovery here reported is that of the long conducting paths. So far as I know, no one has pointed out their unbroken nature, or their tendency to take over the control of the bowel after anoxemia has injured the functions of the synaptic nervous system. Neither has anyone discussed in the light of modern neuro-humoral theory the gradual release from inhibition which can be demonstrated in the bowel after stoppage of the circulation or section of the extrinsic nerves. The facts of observation suggest that the inhibitor may be a chemical substance such as was demonstrated by Finkelman. After the death of the animal it may gradually be destroyed or it may diffuse out of the tissues.

Anyone who will look through a microscope at a well stained specimen of the myenteric plexuses will realize in a moment how almost impossible it is for the histologist to unravel the structure of that maze of fibrils. One might as well try to map the electrical systems of New York City after looking into a few manholes. The physiologist will probably then have to find for himself the answers to the many questions that he is inclined to ask about the nervous system of the bowel. Perhaps the pharmacologist will be able to help but some doubt must always remain as to what his drugs really did to nerves and muscles.

In my own experiments, atropine, cocaine, strychnine, lead and botulinus toxin seemed to be without effect on the peristaltic rushes.

The results of my work on rabbits agree fairly well with some conclusions of Henderson (1933), who worked mainly with guinea-pigs. Unfortunately, I do not know how closely one can compare the fast rushes in rabbits with the slower waves which are obtained on distending the intestine of the guinea-pig. The waves in the guinea-pig appear to resemble those that I learned years ago to produce in the rabbit by obstructing and distending a segment of bowel. They travel slowly and do not much resemble rushes. I called them "obstruction waves."

Henderson found that under adverse conditions, the traveling waves observed in the bowel of the guinea-pig stopped some time before the rhythmic movements did. He found also, as did Bayliss and Starling long ago, that nicotine interfered with the traveling waves but not with the rhythmic movements. He noticed that contractions of the intestinal muscle produced locally by a pinch did not spread along the bowel, and he concluded, as I have done, that when there is rapid spreading of an impulse this must be mediated by nerves. Henderson saw also that the moving column of fluid might help in producing a peristaltic type of wave.

Hukuhara (1933) (35, 36), using rabbits, found that peristalsis continued for about thirty minutes after stoppage of the circulation. In the guinea-pig it lasted for from thirty to forty minutes.

In agreement with my findings were those of Finkleman who, while studying excised small bowel and mesentery of the rabbit found that electric stimulation of the nerves on a mesenteric artery would sometimes, for a few minutes, produce contraction of the bowel; after that it produced inhibition for four hours or more. This suggests that a synapse between preganglionic fibers and the intestinal plexuses soon lost its power to function, while the postganglionic fibers and their endings in the muscle survived for some time.

SUMMARY

An attempt has been made to throw light on the structure and function of the enteric nervous system by measuring the intervals between the stoppage of the circulation and the disappearance of the several motor functions of the bowel. The tissues were kept at a temperature between 37° and 38° C., and whenever the bowel was separated from its blood supply the surrounding medium was aerated or oxygenated. The animal used was the rabbit.

In the autonomic nervous system impulses continue to pass through ganglions for from ten to twenty minutes after the death of the animal; vagus nerve endings in the heart stop functioning after about forty minutes, while the accelerator nerves continue to work for a few minutes longer.

With the bowel left in connection with the mesentery, peristaltic rushes cease the moment the circulation stops. This stoppage is produced by inhibition, perhaps humoral in origin. When the aorta or superior mesenteric artery was clamped or the bowel was cut away from the mesentery, rushes continued to travel during intervals as long as thirty-seven minutes.

Peristaltic rushes appeared to be dependent largely on a nervous synaptic mechanism, which probably did not survive for more than forty minutes after the circulation was shut off. The mechanism was severely injured by nicotine but seemed to be unaffected by atropine, cocaine, strychnine, lead, and botulinus toxin.

The synapses between the vagal and the enteric neurones continued to conduct for from ten to twenty-seven minutes after the stoppage of the circulation.

If normal peristaltic rush is dependent on a synapse highly sensitive to anoxemia, then the rushes which were sometimes observed an hour or more after the death of the animal must have been maintained by supplemental mechanisms. One of these is the moving column of fluid in the lumen of the bowel. That another important one is the "polarity" of the muscular wall or the gradient of forces was shown by the fact that waves in anoxemic bowel could not be made to run orad nearly as far as they ran caudad. Unfortunately, at times it was hard to tell atypical from

typical rushes even with the help of recording apparatus.

Apparently normal rushes were observed occasionally when the whole bowel was excised and kept in Locke's solution, showing that the directing mechanisms are located in the gut itself.

There appear to be at least four conducting systems in the small bowel of the rabbit. First, there are the fine nerve fibrils (histologically demonstrated) that presumably enable thousands of muscle fibers in a short segment of bowel to contract as a unit so as to produce the to-an-fro swaying movements. These fibrils are highly resistant to anoxemia and to the action of nicotine. Second, there appear to be short tracts which mediate conduction over distances averaging 15 cm. They are resistant to moderate doses of nicotine and they survive the loss of the circulation for about 100 minutes. They are injured by degenerative section of the splanchnic nerves. Third, there are long pathways, running the length of the bowel and also through the mesentery. The fact that they are immune to the action of nicotine and highly immune to anoxemia indicates that they are unbroken by synapses. Fourth, there are pathways, apparently broken by synapses, which have much to do with the peristaltic rushes. They are sensitive to nicotine and to anoxemia.

In health, the intestinal muscle is constantly held in check by some inhibiting influence, possibly a chemical one. This influence begins to fade out when the animal dies, or when the bowel is removed from the body; much is lost after about thirty minutes of anoxemia, and still more is lost during the next hour or two. As the inhibitor disappears, the bowel tends more and more to respond in a systolic way to impulses arriving by way of the long, unbroken nerve tracts. Normally the muscle responds only slightly to these impulses.

Nerve endings in the bowel were highly resistant to anoxemia and nicotine.

Segments of bowel kept cyanotic and pulseless for from four to twelve hours appeared to be functioning normally three weeks later. Rushes passed through them in an apparently normal manner.

The intestinal muscle continued to contract rhythmically after anoxemia had apparently put an end to the functions of the nervous system. The rate of contraction became slowed as soon as the circulation failed, and it was slowed after degenerative section of either the vagus or the splanchnic nerves, or of both sets together. The normal rate of rhythmic contraction seemed to be kept at a high level by influences coming from the extrinsic nerves of the bowel. These influences seemed to persist until the sectioned nerves degenerated.

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Studies on the Gastric Hunger Mechanism*

II. The Inhibitory Effect of Dextrose Solutions

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IN the first published report of these studies, Manville and Chuinard (1) showed that dextrose is capable of inhibiting gastric secretion as well as motility. Lim (2) demonstrated fat also to be inhibitory to these gastric activities. While it is well recognized that dextrose can inhibit the motility of the stomach, the evidence in regard to a similar effect on secretion is not yet commonly accepted although Miller and his associates (3) as long ago as 1920, reported that concentrated glucose was capable of depressing gastric secretion. The inhibition of gastric motility probably depends on a humoral mechanism (4). The vagi are not essential as Templeton and Quigley (5) observed inhibition of motility of a Heidenhain pouch and Quigley and Halloran (6) reported inhibition of motility in a vagotomized animal. The present study was undertaken to further the observations of Manville and Chuinard (1) and extended to include the effect of dextrose on secretion induced by various types of stimuli.

METHODS

Dogs with ileogastrostomies were used. Under ether anesthesia, the abdomen was opened, the ligament of Treitz identified and a segment of jejunum about six inches long and supplied with blood from a primary arcade of the superior mesenteric artery was chosen. This segment was resected and an end-to-end anastomosis of the small bowel performed. The distal end of the resected segment was attached to the edges of an opening on the anterior surface of the stomach near the greater curvature. The proximal end was sewed to all layers of the body wall in the operative incision. With this sort of a fistula, dogs have been kept alive and healthy for as long as five years. At autopsy, the gastric mucosa and the mucosa of the fistulous tract are grossly normal.

Before each experiment, food was withheld for twelve to thirty-six hours. A preliminary period of gastric lavage was always observed. The purpose of this was to cleanse the stomach of any residue and to determine whether or not there was active secretion (stimulation) of gastric juice and active motility. Experiments were not conducted unless gastric motility, tonus and secretion were absent or constant at a low level. The dogs were trained to lie quietly during the experiment. Through the fistula, a rubber tube was introduced on the end of which was a light rubber balloon. The outer end of the tube was connected to a chloroform manometer whose float recorded pressure variations on a smoked drum. A catheter with the closed end perforated by a number of openings also was inserted through the fistula. Between operations, the outer end of the catheter was kept closed with a clamp. At five minute intervals, the clamp was removed, the gastric contents aspirated and 50 c.c. of the wash solution were introduced. Tap water and five, ten, twenty and twenty-five per cent dextrose at body temperature were used as wash solutions. The pH of the aspirated gastric contents was determined colorimetrically and a 10 c.c. portion was titrated with N/40 NaOH to determine free and total acid. Topfer's reagent and phenolphthalein were used as indicators. The amount of gastric contents aspirated was recorded as "c.c. returned." Variations in this, coupled with the record on the smoked drum, gave information concerning gastric motility and tonus. The titration values of the gastric contents gave information about the relative amount of HCl secreted during the five-minute period the sample was in the stomach.

For the acidity (secretory) curve, results were charted by plotting cubic centimeters of alkali used against time. For the motility curve, the cubic centimeters returned were plotted against time. The motility curve was inverted in all the graphs and the distance above the ordinant considered an indication of motor activity—the higher the curve, the greater the motility or tonus.

Gastric activity was stimulated by starving for 24 hours; by injection of histamine; pilocarpine HCl, or by injection of insulin.

The method of determining gastric secretory activity used in this work is open to some criticism. The examination of stomach contents at the end of a period of time is not a true indication of the secretory activity of the stomach during that period, but is rather an indication of the end result of all additions to and subtractions from the stomach contents during the interval between aspirations. Additions to the gastric contents may be made via the fistula, swallowing, regurgitation from the duodenum as well as secretion from the gastric mucosa. Subtractions from the stomach may take place via the pylorus; leakage from the fistula, which is usually unimportant; vomiting with which we have not had to contend; and absorption from the stomach which is usually not considered important. However, the principles involved in this method and the difficulties with which we contended are the same as those used and met by other investigators in clinical and laboratory practice. The results may, therefore, be considered comparable.

EXPERIMENTAL

The action of physiological doses of histamine is to produce a large amount of gastric juice of high

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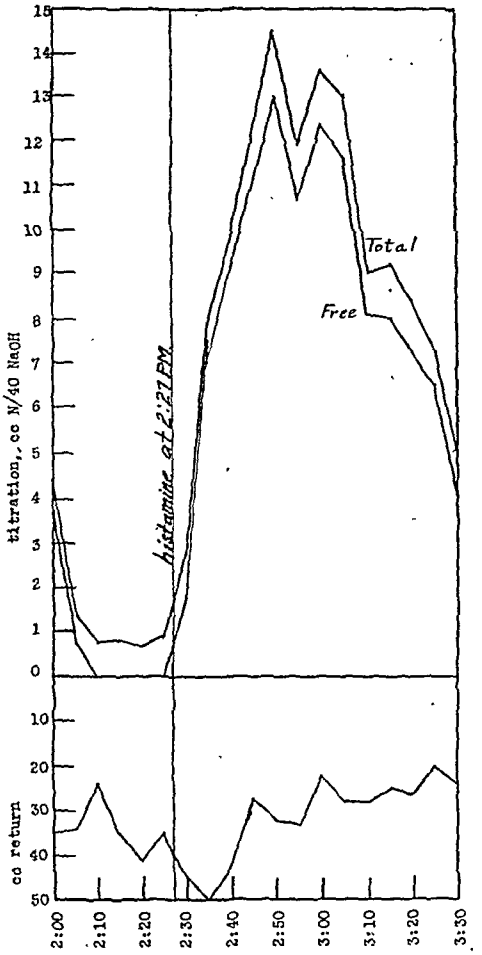


Fig. 1. *Joe, 3/19/36. One mg. histamine at 2:27 p. m.* Water wash used throughout.

acidity. Others (7) have shown that histamine has no power of stimulating pepsin secretion, or of producing any effect on gastric motility (8).

In one series of experiments, gastric secretion was stimulated by the intramuscular injection of one mg. of histamine. When a water wash was used, the secretion induced by histamine reached its maximum in about 35 minutes. When ten per cent dextrose was used as a wash, the maximum secretion was reached much later, the titration values were much less and the maximum secretion tended to be a plateau rather than a peak. For the sake of brevity only typical experiments will be presented.

Histamine stimulation and water wash. Protocol I,

TABLE I

No.	Time In	Time Out	C.C. Out	Titration Free	Titration Total	pH
1	1:56	2:00	35	3.65	4.40	1.0—
2	2:01	2:05	34	0.7	1.4	2.4
3	2:06	2:10	24	0.0	0.7	4.2
4	2:11	2:15	35	0.0	0.8	4.4
5	2:16	2:20	41	0.0	0.65	4.4
6	2:21	2:25	35	0.0	0.9	4.0
7	2:28	2:30	45	1.8	2.8	2.0
8	2:31	2:35	50	7.0	7.9	1.0—
9	2:36	2:40	42	9.0	9.9	1.0—
10	2:41	2:45	27	10.9	12.1	1.0—
11	2:46	2:50	32	13.0	14.5	1.0—
12	2:51	2:55	33	10.7	11.9	1.0—
13	2:56	3:00	22	12.4	13.6	1.0—
14	3:01	3:05	28	11.6	13.0	1.0—
15	3:06	3:10	28	8.1	9.0	1.0—
16	3:11	3:15	25	8.0	9.2	1.0—
17	3:16	3:20	26	7.2	8.4	1.0—
18	3:21	3:25	20	6.5	7.25	1.0—
19	3:26	3:30	21	4.1	5.1	1.0—

Water wash used throughout. One mg. histamine given at 2:27 P. M. Ten c.c. of gastric contents titrated with N/40 NaOH. Titration values are c.c. of NaOH used.

Joe, March 19, 1936. Fig. 1, Table I. Joe is a healthy, very active young male dog weighing about 13 kg. At the start of this experiment (2 p.m) the stomach was empty and quiescent. There was some residual acidity but as soon as this was washed out, the gastric secretion was seen to be very low, there being no free and very little total acid. One milligram of histamine (ergamine acid phosphate, Burroughs Wellcome) was injected intramuscularly at 2:27 p.m. resulting in an almost immediate rise in both free and total acid. The acid value of the gastric contents rose rapidly and

TABLE II

No.	Time In	Time Out	C.C. Out	Bile	Titrations Free	Titrations Total	pH
1	10:53	10:54	44		2.07	4.10	3.2
2	10:42	10:47	20		2.50	3.40	2.0
3	10:55	10:56	43		2.10	2.75	1.9
4	10:57	10:59	21		2.90	2.50	1.8
5	11:00	11:02	38		4.20	6.22	1.6
6	11:10	11:15	70	tr	6.30	7.65	1.2
7	11:16	11:20	70		6.10	7.30	1.2
8	11:23	11:25	55		4.07	5.45	1.4
9	11:27	11:30	50		4.25	6.00	1.4
10	11:35	11:35	22		5.90	6.30	1.6
11	11:37	11:40	41		6.00	6.50	1.6
12	11:43	11:45	50		5.25	6.70	1.4
13	11:48	11:50	42	tr	6.10	7.15	1.2
14	11:51	11:53	54		4.45	6.60	1.4
15	11:56	11:58	48		4.95	6.70	1.4
16	12:02	12:03	45		4.80	6.75	1.4
17	12:07	12:11	21.5		4.65	6.25	1.4
18	12:13	12:15	47		5.05	6.20	1.4
19	12:18	12:20	45		4.75	6.50	1.3
20	12:24	12:28	41		4.60	6.40	1.6

Water wash used until 11:00 A. M. when 10% dextrose wash was started. One mg. histamine given at 11:07 A. M. Titration same as Table I.

reached its highest point 22 minutes after injection of histamine. When the experiment was discontinued

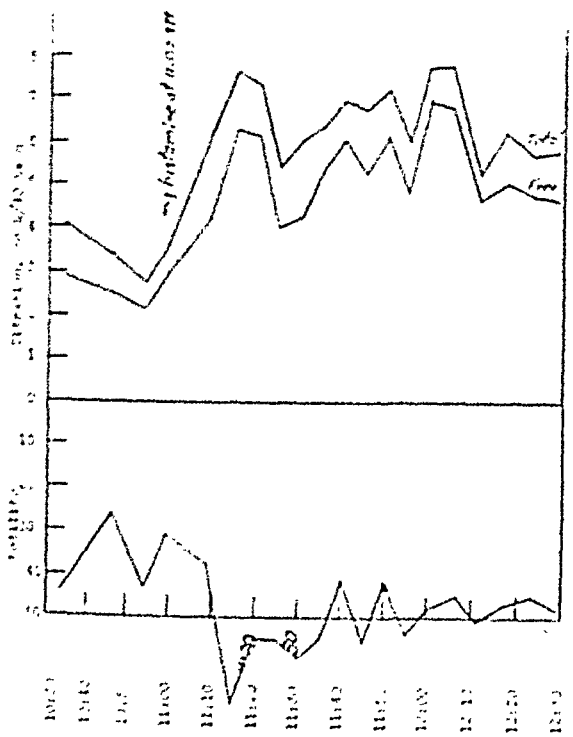


Fig. 2. Joe, 12/6/35. Water wash until 11:00 a. m. One mg. histamine given at 11:00 a. m. and 10% dextrose wash started. Note the effect of the dextrose on motility.

one hour and three minutes after histamine stimulation, the acid values were still high but were coming down. The acid values did not fall as fast as they rose. The pH which was initially above 4.0 fell rapidly to less than 1.0 which is the lower limit of the colorimetric pH set used. This experiment shows very well the effect of histamine in stimulating the secretion of HCl. Histamine has very little if any, effect on the motor activity of the stomach since the tracing shows no significant variations and the returns from the stomach show a marked uniformity. The increase in gastric tonus associated with the shivering caused a slight increase in the emptying ability of the stomach. It is probable, furthermore, that water is incapable of altering the motility of the stomach.

Histamine stimulation and ten per cent dextrose wash. Protocol II, Joe, December 6, 1935, Fig. 2, Table II. This is the same animal as described in Protocol I. Before histamine stimulation there was some acid secretion but it was occurring at a constant rate. One milligram of histamine was given at 11:00 a.m. and 10% dextrose was started as the wash solution. The histamine resulted in a stimulation of gastric secretion. The acid values rose slowly and the high point of the curve was reached at 12:07 p.m., 67 minutes after histamine stimulation. At 11:15 a.m., 15 minutes after histamine stimulation, the free acid value was 6.3 and the total acid value was 7.65. The pH was 1.2. These are to be contrasted with a free acid value of 13.0, a total acid value of 14.5 and a pH of 1.0 twenty-three minutes after histamine stimulation with water only as the wash solution. The preceding protocol showed that histamine alone or histamine and water have very little, if any, influence on gastric motility. In this experiment, there was a

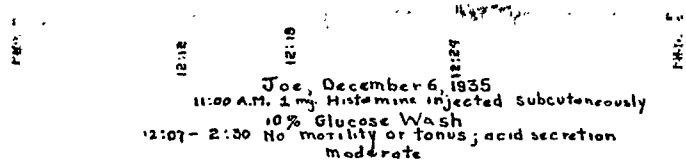


Fig. 2

definite drop in gastric tonus which allowed all the wash solution to return in five minutes. The conclusion, therefore, was reached that the drop in tonus was due to the 10% dextrose which was used as the wash solution. The typical action of dextrose in the upper gastro-intestinal tract seems to be that of inhibiting tonus, gastric motility and secretion.

Comment. Figure 3, (Table III) an average curve, shows definite inhibition of histamine stimulation by 10% dextrose. It is noteworthy that this concentration of dextrose did not completely inhibit the secretory effect of histamine. The method by which histamine stimulates gastric secretion is apparently through vasodilation, thus allowing a freer flow of blood to the glands of the gastric mucosa (8). If this explanation for the effect of histamine can be entirely accepted, then dextrose in the upper gastro-intestinal tract must act either by inhibiting vasodilatation or by preventing gastric motility and secretion in a manner analagous to the action of atropine on the submaxillary gland after stimulation of the chorda tympani. It should be noted also that the fluid removed from the stomach washed with dextrose was greater than the amount introduced. Very little of the sugar solution, therefore, could have reached the duodenum. This point will be commented upon later.

Pilocarpine HCl stimulation and water wash. Protocol III. Pinky, April 23, 1936. Fig. 4, Table IV. Pinky is a young, active male dog, weighing about 13 kg. This animal had an ilio-gastrostomy in November, 1935, and has remained in excellent health since. He is very cooperative. At the beginning of this experiment (10:49 a.m.) due to moderate tonus, the stomach was emptying rapidly but there was no secretion. The preliminary water washes apparently decreased the tonus during the first 21 minutes without increasing the secretion. Two milligrams of pilocarpine HCl

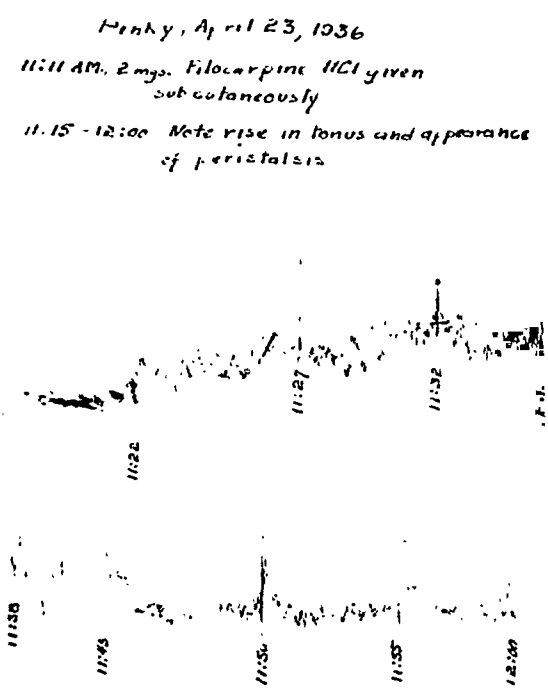


Fig. 3

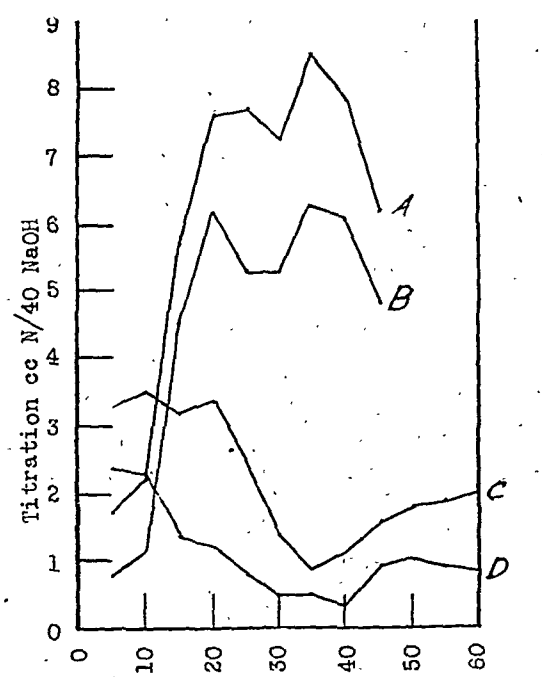


Fig. 3. Average curves with histamine stimulation. A—Total acid with water wash. B—Free acid with water wash. C—Total acid with 10% dextrose wash. D—Free acid with 10% dextrose wash.

TABLE III

Time Min.	Water Wash		10% Dextrose Wash	
	Free	Total	Free	Total
62	3.4	9.8	5.0	4.5
75	6.2	7.4	5.6	6.1
10	8.5	9.5	4.9	7.7
15	9.4	10.4	6.4	10.5
20	13.4	13.5	7.4	9.6
25	13.5	13.7	6.4	6.1
30	13.2	13.4	6.15	7.5
35	12.6	12.6	6.4	7.2
40	7.5	11.5	7.6	7.8
45	9.2	10.2	7.6	8.0
50			7.2	8.1
55			6.5	7.4
60			7.2	8.5
65			7.4	8.2
70			6.4	7.4
75			4.8	7.5
80			4.2	7.6
85			2.2	6.1

Average of experimentally using histamine as the secretory test stimulant. Time is measured from histamine stimulation. 65 time is the time that the histamine was given.

were given at 11:11 a.m. This increased the rate of emptying as well as the secretion of HCl and mucus. Within five minutes the animal was freely discharging serum from the nose and within ten minutes he was quite salivated. Thirty-seven minutes after pilocarpine stimulation, the gastric secretion had reached its maximum. At the peak, the free acid value was 9.5 and the total acid value 12.0. The sharp dip in the secretory curve just before the peak is due to the fact that during the preceding five minute interval the animal swallowed a quantity of saliva (the sample was one-half saliva—usually the saliva drained freely from the side of the mouth). The acid values were still high, but were falling rapidly when the experiment was discontinued at 12:12 p.m., 61 minutes after pilocarpine stimulation. The zone between the free and total acid values was greater than in the histamine experiment thus denoting an increased amount of buffering material.

Pilocarpine HCl stimulation and ten per cent dextrose wash. Protocol IV, Pinky, December 20, 1935.

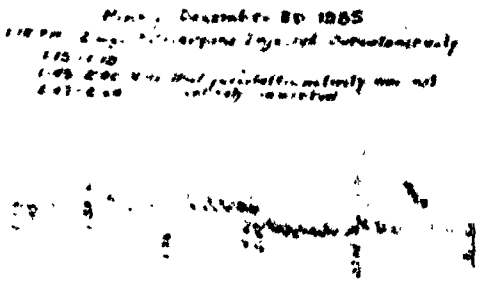


Fig. 4

Fig. 5, Table V. At the start (12:45 p.m.) the stomach was quite tonic, but not motile and there was very little secretion. Plain water was used as a wash until 1:14 p.m., at which time a wash of 10% dextrose was instituted and two mgs. of pilocarpine HCl were given. In spite of a slight initial secretion and the stimulatory effect of the pilocarpine, the secretion of acid never reached a high figure. The acid value of the samples never rose above 4.3 and this high point was reached at 1:18, four minutes after pilocarpine stimulation. Thirty-seven minutes after pilocarpine stimulation, the total acid value was 1.5 with a 10% dextrose wash as contrasted with 12.0 when a water wash was used. Moreover the acid value reached 3.5 at 2:25 p.m., 71 minutes after pilocarpine stimulation. Dextrose of this concentration was only partially effective in decreasing the emptying time of the stomach. The action of pilocarpine on the salivary glands likewise was not completely inhibited.

Comment. Reference to Fig. 6 (Table VI), average curves, shows definitely that 10% dextrose solutions are capable of greatly inhibiting the secretion resulting from pilocarpine HCl stimulation. Whether or not complete inhibition could be obtained by properly balancing the stimulatory effect of pilocarpine against the inhibitory effect of dextrose was not determined. In only one of the experiments using pilocarpine stimulation and 10% dextrose as an inhibitor was the total inhibitory effect of glucose on gastric motility

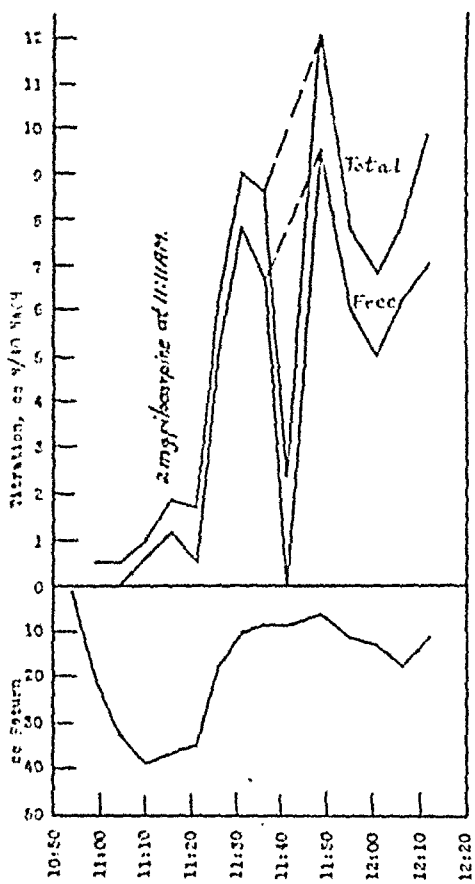


Fig. 4. Pinky, 4/23/36. Two mg. pilocarpine given at 11:11 a. m. Water wash used throughout.

TABLE IV

No.	Time		C.C. Out	Titration	
	In	Out		Free	Total
1	10:49	10:54	1	0.0	—
2	10:55	10:59	20	0.0	0.5
3	11:00	11:04	32	0.0	0.5
4	11:05	11:10	39	0.6	1.0
5	11:12	11:16	36	1.2	1.9
6	11:17	11:21	35	0.5	1.7
7	11:22	11:26	18	5.0	6.1
8	11:27	11:31	10	7.8	9.0
9	11:32	11:36	8	6.6	8.6
10	11:38	11:42	8	0.0	2.4
11	11:43	11:48	6	9.5	12.0
12	11:50	11:55	11	6.0	7.8
13	11:57	12:01	13	5.0	6.8
14	12:02	12:06	18	6.1	7.8
15	12:08	12:12	11	7.0	9.8

Water wash used throughout. Two milligrams of Pilocarpine HCl given at 1:11 A. M. Titration same as in Table I.

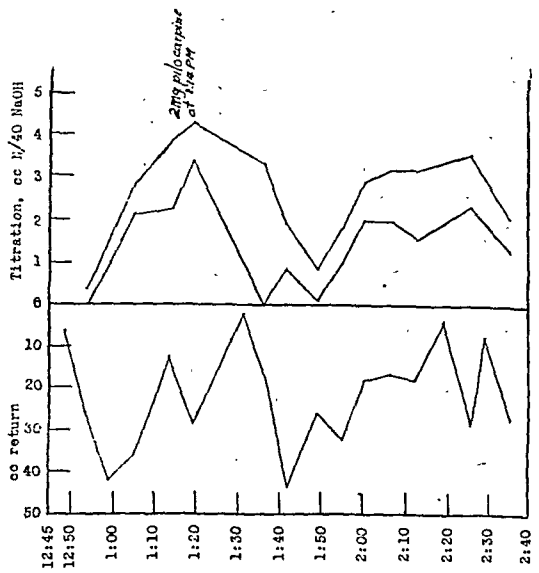


Fig. 5. Pinky, 12/20/35. Water wash used until 1:14 p. m. Two mgs. pilocarpine given at 1:14 p. m. and 10% dextrose wash started.

apparent. Pilocarpine acts by stimulation of the myoneural junctions of the cranio-sacral autonomic system (9). It acts first upon the vagus by stimulating both gastric secretion and motility. Ten per cent dextrose solutions are capable of more effectively inhibiting the secretion induced by pilocarpine than the motor activity resulting from this type of stimulation. The inhibitory effect of dextrose on mucus secretion is as apparent as on acid secretion as can be seen by comparing the width of the zone between the curves for free and total acid.

Insulin stimulation and water wash. Protocol V. Pinky, September 16, 1936. At the beginning of the experiment there was no secretion of free acid and the total acid values were at or below 0.6 c.c. of N/40 NaOH. There was no motility and the tonus was insufficient to expel much of the wash fluid into the

TABLE V

No.	Time		C.C. Out	Mucus	Titration		pH
	In	Out			Free	Total	
1	12:43	12:48	6	—	—	—	6.0
2	12:48	12:53	26	—	0.0	0.4	5.4
3	12:54	12:59	42	—	1.0	1.65	3.2
4	1:00	1:05	36	—	2.1	2.85	3.0
5	1:08	1:13	12	—	2.3	3.9	3.0
6	1:14	1:19	29	—	3.4	4.3	3.2
7	1:20	1:31	2	—	—	—	3.4
8	1:31	1:36	17	11	0.0	3.3	3.4
9	1:37	1:42	44	4	0.9	1.95	3.4
10	1:45	1:49	26	3	0.15	0.9	4.0
11	1:50	1:55	32	—	1.05	1.8	3.4
12	1:56	2:00	18	—	2.0	2.9	3.2
13	2:01	2:06	16	—	2.0	3.2	3.0
14	2:07	2:12	18	1	1.6	3.2	3.0
15	2:14	2:19	4	—	—	—	4.0
16	2:20	2:25	28	—	2.4	3.6	3.2
17	2:26	2:29	7	—	—	—	3.2
18	2:30	2:35	27	—	1.3	2.1	3.0

Water wash used until 1:14 P. M. at which time the ten per cent dextrose wash was started. Two milligrams of Pilocarpine HCl were given at 1:14 P. M.

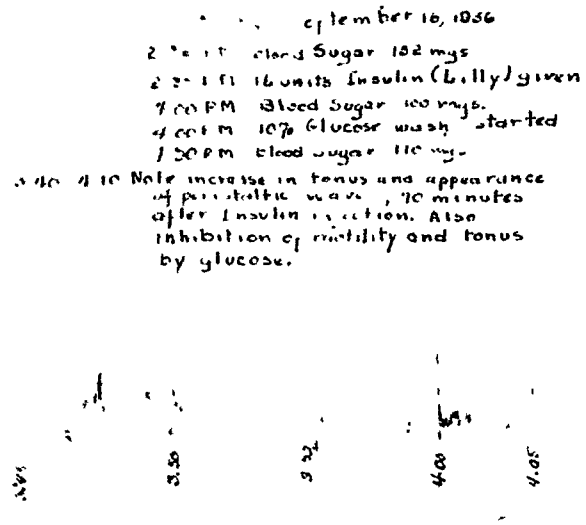


Fig. 5

duodenum. After washing the stomach four times and finding no evidence of gastric activity, a sample of blood was taken for a blood sugar determination and 16 units of insulin were given subcutaneously (2:35 p.m.).

The blood sugar was found to be 123 mg. per cent. The next forty minutes were entirely devoid of any evidence of gastric activity. At 3:10 p.m. the acid values began increasing. Tonus and motility also began improving at this time as shown by the graphic record of the decreasing returns of wash water. From 3:10 p.m. to 4:10 p.m., there was a steady increase in the output of acid until the maximal amount of 16.8 c.c. free and 21.8 c.c. combined acid were reached. Up until 3:50 p.m., however, there was no increase in tonus or motor activity—at least not enough to affect the return of wash water. Forty minutes after secretion began increasing, there was a definite and marked increase in the emptying power of the stomach. At 4:00 p.m., the blood sugar was 100 mgs. per cent. Five minutes later (4:05 p.m.) and thereafter ten per cent dextrose solution was used for washing out the stomach. For the next five minutes the glucose was without effect since the stomach emptied as rapidly as before and the acid secretion reached its highest level. Immediately thereafter, however, acid production began subsiding so that at the end of the experiment (4:45 p.m.) the values were 1.8 c.c. of free and 2.4 c.c. of total acid. There was no effect on motility or tonus until 4:35 p.m. or 25 minutes after acid secretion began diminishing. At the end of the experiment nearly half the wash solution was recovered. Thus dextrose inhibits the gastric motor and secretory activity induced by insulin. There is, however, a dif-

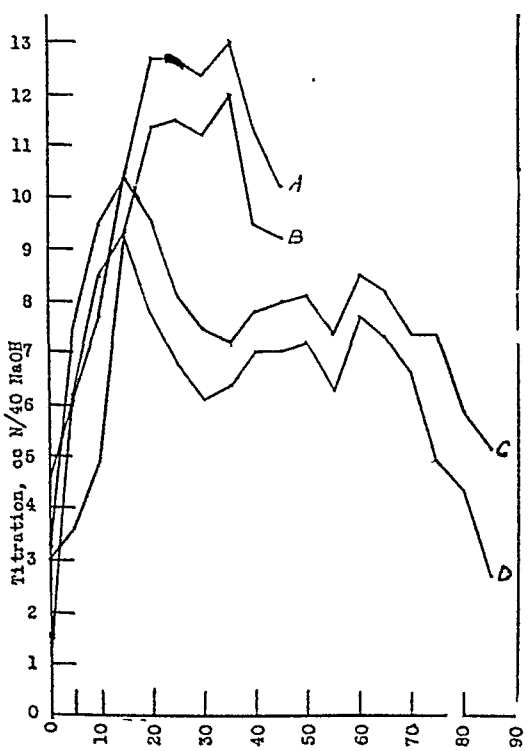


Fig. 6. Average of experiments using 2 mgs. pilocarpine as stimulant, given at 0 time. A—Total acid with water wash. B—Free acid with water wash. C—Total acid with 10% dextrose wash. D—Free acid with 10% dextrose wash.

TABLE VI

Time	Water Wash		10% Dextrose Wash	
	Free	Total	Free	Total
5	0.8	1.75	2.4	3.3
10	1.1	2.22	2.3	3.5
15	4.5	5.7	1.4	3.2
20	6.2	7.6	1.2	3.4
25	5.3	7.7	0.8	2.5
30	5.3	7.3	0.5	1.4
35	6.3	8.5	0.5	0.8
40	6.1	7.8	0.4	1.1
45	4.8	6 2	0.9	1.6
50	—	—	1.0	1.8
55	—	—	0.9	1.9
60	—	—	0.8	2.0

Averages of all experiments using two milligrams of Pilocarpine HCl as stimulus. Time is measured from Pilocarpine HCl stimulation.

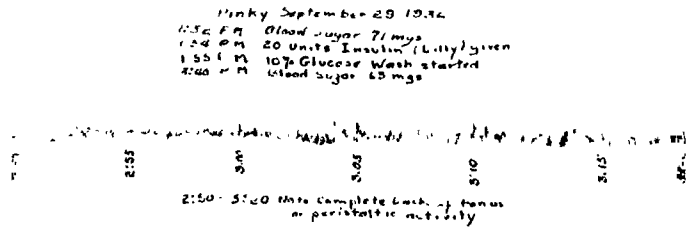


Fig. 6

ference in the time of appearance of the two effects—secretion being more easily influenced than muscular activity. This confirms the findings published in the first report.

At the end of the experiment the blood sugar was found to be 110 mg. per cent. About 235 c.c. of ten per cent dextrose solution entered the duodenum before any inhibitory effects were noted. Altogether approximately 324 c.c. of the sugar solution entered the duodenum to account for the slight rise in blood sugar. It is interesting to note the definite presence of gastric secretory and motor activity with a blood sugar of 100 mgs. per cent and a complete subsidence of these activities with a blood sugar only 10 mg. per cent higher. This is further confirmation of the statements made in the first report.

Insulin stimulation and ten per cent dextrose. Protocol VI. Pinky, September 29, 1936. Fig. 8, Table VIII. In this experiment, 20 units of insulin were administered subcutaneously and a ten per cent dextrose wash used throughout. Three preliminary washes between 1:30 p.m. and 1:45 p.m. showed no acid production, no motility (peristalsis) and very little tonus. The blood sugar at 1:52 was 71 mgs. per cent. The

TABLE VII

No.	Time		C.C. Out	Titration	
	In	Out		Free	Total
1	2:13	2:18	40	0.0	0.5
2	2:18	2:25	47	0.0	0.6
3	2:25	2:29	49	0.0	0.4
4	2:30	2:35	48	0.0	0.3
5	2:35	2:40	49	0.0	0.3
6	2:40	2:45	48	0.0	0.3
7	2:45	2:50	50	0.0	0.3
8	2:51	2:55	50	0.0	0.25
9	2:55	3:00	50	0.0	0.3
10	3:00	3:05	49	0.0	0.25
11	3:05	3:10	40	0.0	0.3
12	3:10	3:15	28	0.2	0.55
13	3:15	3:20	15	1.0	1.35
14	3:20	3:25	30	1.1	1.4
15	3:25	3:30	35	1.4	1.9
16	3:30	3:35	32	1.5	1.9
17	3:35	3:40	43	1.8	2.3
18	3:40	3:45	40	1.5	2:05
19	3:45	3:50	21	3.6	4.1
20	3:50	3:55	5	10.0	11.5
21	3:55	4:00	4	12.4	14.8
22	4:00	4:05	3	10.0	12.2
23	4:05	4:10	5	16.8	21.8
24	4:10	4:15	2	13.0	15.5
25	4:15	4:20	3	6.8	8.8
26	4:20	4:25	3	5.0	5.5
27	4:25	4:30	2	3.2	4.5
28	4:30	4:35	10	3.5	4.8
29	4:35	4:40	12	2.1	2.7
30	4:40	4:45	21	1.8	2.4

Sixteen units of insulin were given subcutaneously at 2:35 P. M. Water wash was used until 4:05 P. M. when it was replaced by ten per cent dextrose.

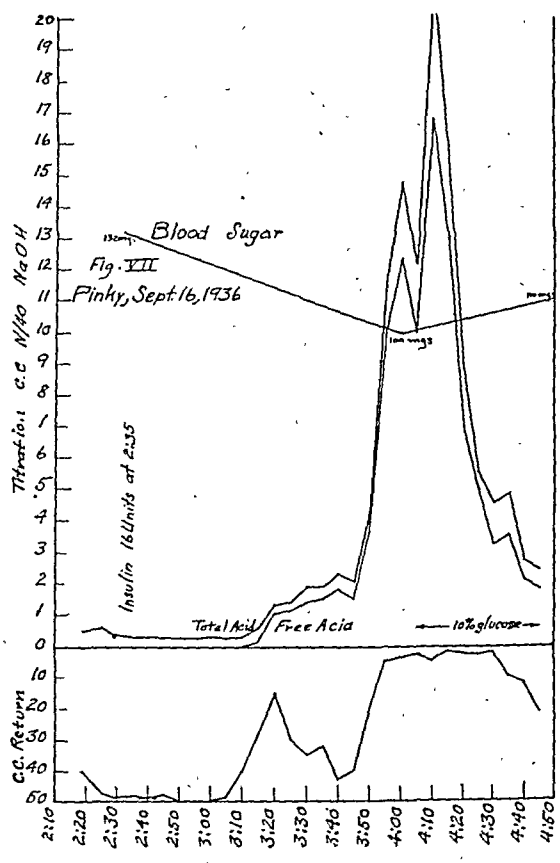


Fig. 7

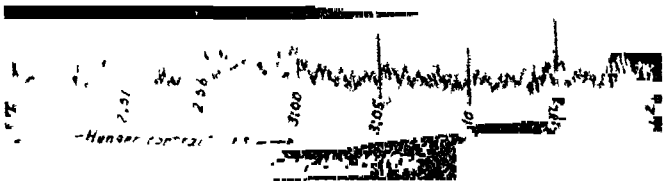


Fig. 7

insulin was given at 1:54 and the sugar wash instituted at 1:55 p.m. During the entire experiment there was no evidence of gastric stimulation of any sort. Although a total of 1,000 c.c. of ten per cent dextrose solution were placed in the stomach, only approximately 91 c.c. entered the duodenum. The nine grams of dextrose thus obtained were insufficient to effect the blood sugar which at 3:40 p.m. was 63 mgs. per cent. Aside from showing the inhibitory effect of dextrose on gastric activity induced by insulin, this experiment shows the lack of gastric motility when the blood sugar is at a low level. Thus the stimulatory effect of 20 units of insulin is not as effective in the presence of dextrose in the stomach as is 16 units when given alone.

Comment. (Fig. 9, Table IX). It is well known that insulin is a powerful stimulant to both gastric motor and secretory activity. The use of insulin in non-diabetic malnutrition is based largely on this effect. The first report of this series sets forth clearly the effect of insulin on both of these gastric activities. Presumably insulin acts through stimulation of the vagus. It is not clear whether this stimulation is central or peripheral although what little evidence we have seems to indicate a peripheral action.

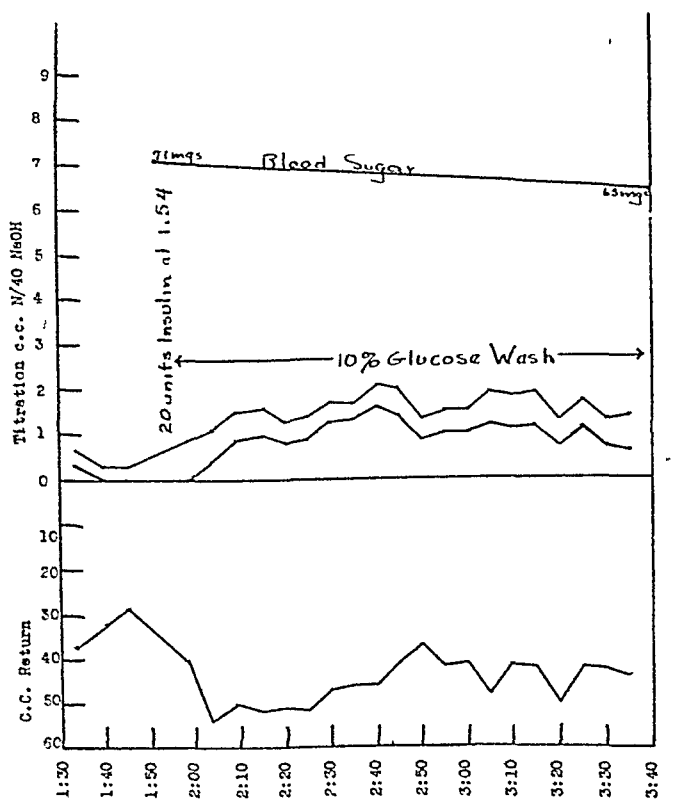


Fig. 8. Pinky, 9/29/36. Twenty units of insulin at 1:54 p. m. Ten per cent dextrose started at 1:54 p. m.

In this group of experiments the animals were given 16 to 27 units of insulin subcutaneously. It will be noted that 20 and 27 units of insulin produces a more effective stimulus than a dose of 16 units. As previously reported, insulin produces a definite increase in gastric secretory and motor activity. It should be noted (Fig. 9 and Table IX) that the inhibitory effect of dextrose was exhibited in the face of a larger stimulating dose of insulin than that used in the experiment where plain water was used as the wash solution. The maximum effect of insulin insofar as secretion and motility of the stomach is concerned occurs in from 45 to 60 minutes after its administration.

Spontaneous hunger contractions. Protocol VII. Pinky, January 14, 1936. Fig. 10, Table X. In this experiment, the graphic record of gastric motility can be divided into six periods: Period I (2:45-3:00) in which hunger contractions were present but no secretion of acid; Period II (3:00-3:20) in which acid was being secreted but little motility evident; Period III (3:20-3:31) reappearance of hunger contractions with a diminution in the acid secreted; Period IV (3:31-3:46) inhibition of motility, tonus and secretion as the result of a twenty per cent dextrose wash; Period V (3:46-4:06) under the influence of water wash the reappearance of tonus and motility with very little increase in secretion of acid; Period VI (4:06-4:16) twenty per cent dextrose solution again used as wash with complete inhibition of motility and

TABLE VIII

No.	Time In	Time Out	C.C. Out	Bile	Titration Free	Titration Total
1	1:30	1:34	37	—	0.3	0.65
2	1:35	1:40	32	—	0.0	0.3
3	1:40	1:45	28	—	0.0	0.3
4	1:55	1:59	40	++	0.0	0.9
5	2:00	2:04	54	tr	0.4	1.1
6	2:05	2:09	50	—	0.9	1.5
7	2:10	2:15	52	—	1.0	1.6
8	2:17	2:20	51	—	0.8	1.3
9	2:21	2:25	52	—	0.9	1.4
10	2:26	2:30	47	—	1.25	1.7
11	2:31	2:36	16	—	1.3	1.65
12	2:36	2:40	46	+	1.6	2.1
13	2:41	2:45	41	—	1.4	2.0
14	2:46	2:50	37	—	0.85	1.3
15	2:51	2:55	42	+	1.0	1.5
16	2:56	3:00	41	tr	1.0	1.5
17	3:01	3:05	48	++	1.2	1.9
18	3:06	3:10	41	+	1.1	1.8
19	3:11	3:15	42	++	1.15	1.9
20	3:16	3:20	50	+	0.7	1.3
21	3:21	3:25	42	tr	1.1	1.75
22	3:26	3:30	43	+	0.7	1.3
23	3:31	3:35	44	tr	0.65	1.4

Twenty units of insulin were given subcutaneously at 1:54 P. M. Except for the three washes prior to insulin administration, ten per cent dextrose was used as wash throughout.

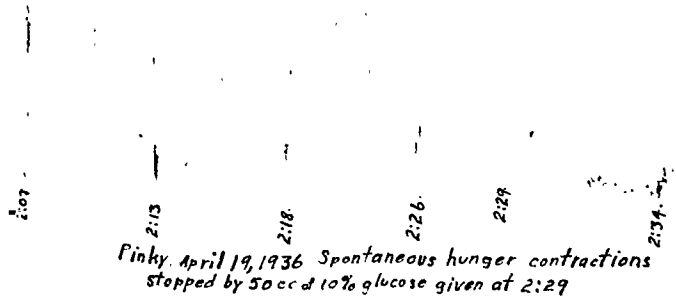


Fig. 8

tonus. Twenty per cent dextrose solution is thus inhibitive to psychic secretion as well as hunger contractions. When muscular activity of the stomach during hunger is in evidence, there may be only slight evidence of secretory activity. Vice versa, when muscular activity is absent, secretion may be occurring. A twenty per cent dextrose solution inhibits both.

Protocol VIII. Pinky, April 19, 1936. Fig. 11, Table XI. At 1:55 p.m., this animal's stomach was exhibiting powerful hunger contractions. The first wash fluid showed no free or total acid. The stomach was emptying so completely in five minute periods that the wash water was run in and out again with no intermediate pause. No free acid was found and very little total. At 2:29 and 2:34 p. m., fifty c.c. of ten per cent dextrose solution was used as a wash water. Five minutes later motility and tonus were almost completely inhibited. Acid production still was almost nil.

Apparently, then, there may be a complete dissociation between gastric motor and gastric secretory activity in that an actively motile stomach which is

TABLE IX

Time	Water Wash		10% Dextrose Wash	
	Free	Total	Free	Total
00	0.0	0.3	0.0	0.9
05	0.0	0.3	0.4	1.1
10	0.0	0.3	0.9	1.5
15	0.0	0.25	1.0	1.6
20	0.0	0.3	0.8	1.3
25	0.0	0.25	0.9	1.4
30	0.0	0.3	1.25	1.7
35	0.2	0.55	1.3	1.66
40	1.0	1.35	1.6	2.1
45	1.1	1.4	1.4	2.0
50	1.4	1.9	0.85	1.3
55	1.5	1.9	1.0	1.5
60	1.8	2.3	1.0	1.5
65	1.5	2.05	1.2	1.9
70	3.6	4.1	1.1	1.8
75	10.0	11.5	1.15	1.9
80	12.4	14.8	0.7	1.3
85	10.0	12.2	1.1	1.75
90	16.8	21.8	0.7	1.3
95	—	—	0.65	1.4

Average of experiments using insulin as the stimulant. Time is measured from insulin stimulation.

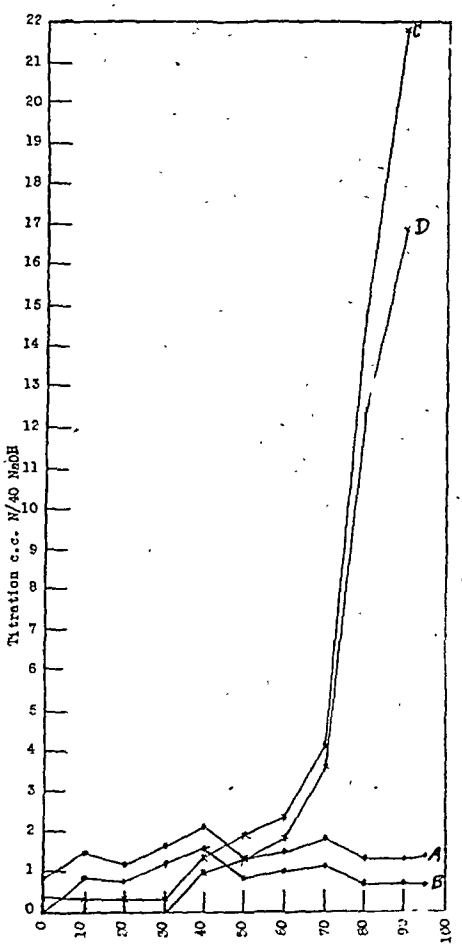


Fig. 9. Average of experiments using insulin as stimulant, given at 0 time. A—Total acid with dextrose wash. B—Free acid with dextrose wash. C—Total acid with water wash. D—Free acid with water wash.

TABLE X

No.	Time In	Time Out	C.C. Out	Bile	pH	Titration Free	Titration Total
Period I.	2:15-3:00 P.M.						
1	2:15	2:50	3	—	—	0.0	—
2	2:51	2:55	2	—	—	0.0	—
3	2:56	3:00	2	tr	—	0.0	—
Period II.	3:00-3:20 P.M.						
4	3:01	3.05	28	tr	2.0	1.0	1.7
5	3:06	3:10	15	tr	2.2	0.9	1.8.
6	3:11	3:15	48	tr	1.8	2.1	2.1
7	3:16	3:20	42	tr	1.1	2.9	1.8
Period III.	3:20-3:31 P.M.						
—	3:20	3:25	—	—	—	—	—
8	3:25	3:30	3	00	—	0.5	1.0
Period IV.	3:31-3:46 P.M.						
9	3:31	3:35	32	00	2.2	1.3	2.05
10	3:36	3:40	59	+	2.1	0.0	1.1
11	3:41	3.45	52	+	2.1	0.0	0.75
Period V.	3:46-4:06 P.M.						
12	3:46	3 50	18	00	2.0	0.1	0.7
13	3:51	3:55	12	00	1.8	0.7	1.35
14	3:55	4:00	32	00	1.8	1.1	1.8
15	4:01	4:05	13	+	2.6	0 0	0.4
Period VI.	4.06-4:16 P.M.						
16	4.06	4:10	33	00	2.6	0.1	1.1
17	4:11	4:16	52	00	2.0	0.6	1.3

Water wash was used until 3:30 P. M. Twenty per cent dextrose solution was used from 3:31 P. M. to 3:45 P. M. Water wash was used from 3:46 P. M. to 4.05 P. M. Twenty per cent dextrose solution was used from 4:06 to the end of the experiment.

emptying rapidly may not be secreting acid, or from the motor standpoint, an actively secreting stomach may be quiescent.

Dissociation of gastric motor and secretory activity. Frequently in the course of the experiments herein described, there was noted what appeared to be a complete dissociation of gastric motor and secretory activity. That is, a motile stomach exhibiting powerful peristaltic waves would not be producing acid, or, at other times, a quiescent stomach would be found actively secreting acid.

The experiments described in the seventh and eighth protocols show the absence of active secretion when hunger contractions were occurring. The data obtained from "Joe" (Table 12, Fig. XII) showed marked secretory activity during complete absence of motility. Furthermore, a ten per cent dextrose wash did not completely inhibit this activity while a stronger solution (25%) exerted the usual inhibitory effect.

TABLE XI

No.	Time In	Time Out	C.C. Out	Titration Free	Titration Total
1	1:55	2:00	3	0.0	—
2	2:04	2:05	16	0.0	0.5
3	2:11	2:12	38	0.0	0.4
4	2:17	2:18	26	0.0	0.4
5	2:24	2:25	18	0.0	0.2
6	2:29	2:30	0	—	—
7	2:33	2:34	0	—	—
8	2:35	2:40	40	0.0	0.3

Water wash was used until 2:29 P. M. from which time ten per cent dextrose solution was used.

In protocol VIII a wash of ten per cent dextrose was sufficient to inhibit hunger contractions. The data in Table XII show ten per cent dextrose solutions had only slight effect on psychic secretion. Only when the cencentration was increased to 25 per cent did a marked inhibitory effect appear. In the experiments where histamine and pilocarpine were used as gastric excitants, it was observed also that ten per cent dextrose was not completely inhibitory. Gastric activity provoked by twenty units of insulin was completely inhibited by a ten per cent dextrose wash. It seems, therefore, that the amount of histamine and of pilocarpine used were more effective stimulants than the quantity of insulin administered. This difficulty, however, should not detract from the conclusion that dextrose solutions are definitely inhibitory to both types of gastric activity. One of the difficulties encountered in these experiments was the balancing of the inhibitant against the stimulant. Since ten per cent dextrose inhibited psychic (hunger) contractions but not psychic (appetite) secretion, one would be inclined to

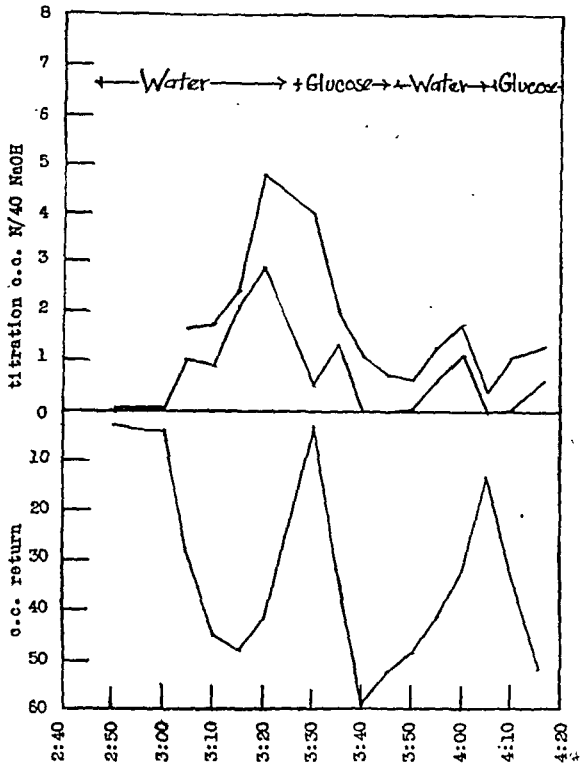


Fig. 10. Pinky, 1/14/36. Spontaneous hunger contractions alternating with secretory activity. Inhibitory effect of 20% dextrose on both types of activity. Motility and secretion do not necessarily occur together.

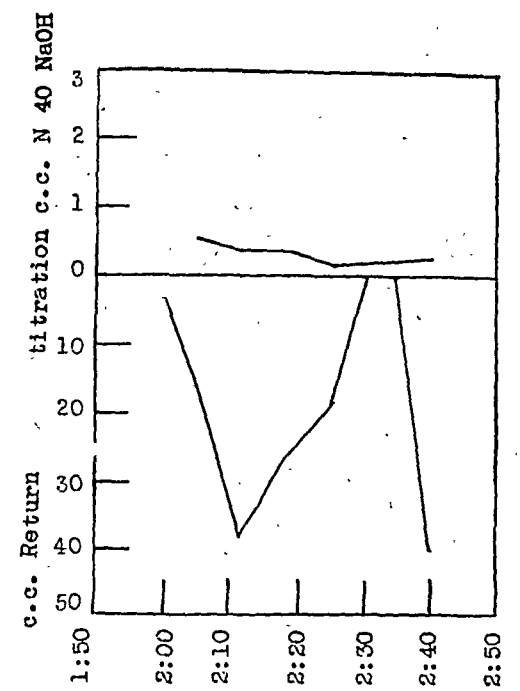


Fig. 11. Pinky, 4/19/36. Spontaneous hunger contractions stopped by 50 c.c. of 10% dextrose given at 2:29 p. m.

conclude that the secretory stimulus is greater than the motor.

Upon the introduction of dextrose solutions into the stomach, there occurred a slight delay before the inhibitory effects were noted. This latent period has been explained as being due to the time required for the glucose to reach the duodenal mucosa where it may bring into existence an inhibiting chalone. Evidence is presented in this paper which may make necessary a revision of this view. In Protocol VI, for example, the stimulatory effect of twenty units of insulin was completely held in abeyance by the ten per cent dextrose solution. Both tonus and peristalsis were at such a low ebb that in the entire experiment only 91 c.c. of the dextrose solution failed to be recovered. We realize that this latter statement is not strictly true since the secretory activity of the stomach, fluids swallowed (saliva) and material regurgitated from the duodenum were not considered. It will be noted that bile was present in the aspirated contents. The low amount of total acid titrated and the narrow margin between the figures for free and for total acid (buffer material) indicate very little alkaline or mucoid material present. Therefore, it may be assumed that the 91 c.c. of ten per cent dextrose that was not recovered represents a fairly close approximation of the quantity of sugar required to exert an effective inhibition. Data of a similar nature are provided in Fig. 12 and Table XII. During the

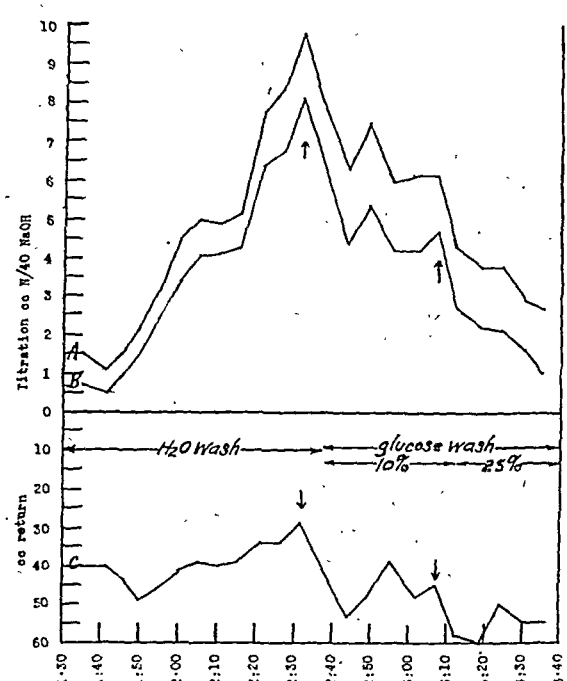


Fig. 12. Joe, 4/30/36. No stimulant used. This experiment shows the dissociation of gastric secretory and motor activity.

TABLE XII

No.	Time In	Time Out	C.C. Out	Bile	Titration Free	Titration Total
1	1:30	1:35	40	——	0.7	1.5
2	1:36	1:41	40	——	0.5	1.15
3	1:41	1:46	44	——	1.0	1.6
4	1:46	1:50	49	——	1.5	2.2
5	1:51	1:55	46	——	2.4	3.1
6	1:56	2:00	41	——	3.4	4.5
7	2:01	2:05	39	——	4.05	5.0
8	2:06	2:10	40	——	4.1	4.9
9	2:11	2:15	39	+	4.3	5.2
10	2:16	2:21	34	+	6.4	7.8
11	2:22	2:26	34	+	6.75	8.4
12	2:27	2:31	29	+	8.1	9.8
13	2:33	2:37	40	+	6.5	8.0
14	2:39	2:44	53	++	4.4	6.3
15	2:45	2:49	48	++	5.4	7.5
16	2:50	2:55	39	tr	4.2	6.0
17	2:57	3:02	48	++	4.2	6.2
18	3:03	3:07	45	tr	4.7	6.1
19	3:08	3:12	58	—	2.7	4.3
20	3:13	3:18	60	tr	2.2	3.8
21	3:19	3:24	50	+	2.1	3.8
22	3:25	3:30	55	++	1.6	2.9
23	3:31	3:36	55	+	1.0	2.6

Water wash was used from 1:30 P. M. to 2:31 P. M. Ten per cent dextrose wash was used from 2:38 P. M. to 3:07 P. M. Twenty-five per cent dextrose wash was started at 3:08 P. M. and used to the end of the experiment.

thirty minutes in which the ten per cent dextrose solution was used, there was a net loss of 27 c.c. or 2.7 grams of sugar. While there was a definite inhibition of secretion, the effect was far from being complete. During the following twenty-five minutes in which twenty-five per cent dextrose was used there was a net gain of 28 c.c., indicating a very small sugar loss, yet inhibition was complete.

We are thus faced with a situation where it seems apparent that a twenty or twenty-five per cent solution of dextrose is a more effective inhibitor than a ten per cent solution. Furthermore, the effectiveness of inhibition depends a great deal upon the strength of the stimulus. Nor does it seem to be dependent upon the amount of dextrose entering the duodenum. Can it be that some of the inhibitory effect is mediated through a gastric mechanism? Undoubtedly this angle of the problem will have to be handled with a much more precise method of procedure.

The inhibition of gastric secretory and motor activity by sugar brings up the question as to how long the inhibitory influence of the glucose solution would last if it were left in the stomach. Our experience indicates that the period of inhibition persists for approximately thirty minutes.

The practical implications of these findings are obvious. The inhibitory effect of dextrose solutions on the human stomach should be determined. On the assumption that there is a gastric residue of 50 c.c., the ingestion of five grams of dextrose would produce a ten per cent solution in the stomach. If there is a twenty-five c.c. residue, a twenty per cent solution would result. The administration of this quantity of dextrose every half hour should, on the basis of the experiments herein described, keep the stomach quiescent. On the Sippy regime, the dextrose only need be given every hour.

SUMMARY

1. Evidence is provided confirming previous observations that dextrose solutions (ten, twenty, twenty-five per cent) placed in the stomach inhibit hunger contractions and that the appearance of gastric motility is not always associated with a drop in blood sugar.

2. Gastric motor activity induced by pilocarpine and insulin are also inhibited by introducing dextrose solutions into the stomach.

3. Gastric secretion provoked by histamine, pilocarpine, insulin as well as psychic secretion also is inhibited by dextrose.

4. Further evidence is presented of a genuine dissociation between the secretory and motor activity of the stomach.

5. The clinical application of these results is discussed.

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Peptic Ulcer Therapy

By

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IN previous work on gastric digestion (1), reference was made by the author to a method of treating peptic ulcers, based on experimental findings in which potential or active alkalis were employed just before as well as after feedings. It was pointed out that complete neutralization of gastric digestion depended on the presence of potential or active alkalis for immediate neutralization of the pepsin-HCl or pepsin-HCl pancreas-bile combination. In such alkalized mixtures digestion of muscle fibers was completely absent. When an interval of 15 minutes or longer was allowed before such neutralization was carried out, complete inhibition of peptic digestion of the meat fibers did not occur.

The usual methods of peptic ulcer treatment, as given by von Leube (2), Lenhartz (3), or Sippy (4), advocate at least a half hour interval between the time of feeding and the administration of neutralizing substances, when these are employed. Such treatment does not prevent digestion of the gastric or duodenal content, and probably interferes with healing of the ulcer to some extent. When alkalis are administered before as well as after feedings, to the point that digestion of meat fibers, as demonstrated by our method of stool examination (1), is decreased to 10 to 30 per cent, rapid relief of symptoms (within 72 hours after proper dosage) and apparent healing of the peptic ulcers has been noted. Sufficient time has not elapsed to determine the permanency of these results, since these patients have all been treated within the past five years.

In this group of cases, ambulatory treatment has been employed except where active hemorrhage has necessitated two to three week periods in bed. Since continuous gastric analysis could not be maintained for the demonstration of complete inhibition of gastric digestion by titration methods, recourse was had to frequent stool examinations.

Simultaneous experiments on gastric digestion *in vitro* revealed that the majority of acids tested activated pepsin to varying degrees in its digestion of muscle fiber. Neither nitric nor sulfuric acid, in concentrations producing the same pH as hydrochloric acid, were as effective in promoting digestion with pepsin alone or with the combination of pepsin pancreas-bile, as was the latter acid. Phosphoric, lactic, acetic, boric, salicylic, benzoic, oxalic, tannic, tartaric, citric, and the other acids tested all activated peptic digestion to some degree, and were active also in combination with the pepsin pancreas-bile mixture. Salicylic acid was markedly more active *in vitro* in the pepsin pancreas-bile combination than anticipated from the hydrogen ion concentration. This finding should be kept in mind as a possible explanation of the starting point of some peptic ulcers in humans.

With these findings as a basis, the diet was so arranged that during the first three to eight weeks all foods containing appreciable acid, such as tomatoes, fruits and buttermilk, were eliminated. Other cooked and raw vegetables were permitted. Meats, eggs, fish, fowl, crustaceans, bi-valves, curd or cottage cheese and milk, American or Swiss cheese, were permitted in normal quantities. Bread, tea, coffee and milk in normal quantities were also allowed. Cereals or pureed foods were reduced to a low level in order, so far as possible, to prevent intestinal fermentation.

After the three to eight weeks period, tomatoes, raw or cooked, were permitted along with adsorbent ant-acid powder (to take care of the additional acid) in quantity sufficient to keep muscle fiber digestion down to or below 30% as estimated by stool examination. Gradually, fruits were added to the diet, and in the milder cases, after twelve weeks, the adsorbent ant-acid powder was reduced ½ dram weekly. The 30% level of digestion was maintained during this period. When necessary to achieve this level, the patient was kept on the adsorbent powder for a longer period before the next reduction was made.

Fresh tincture of stramonium was employed before meals and maintained just below the dryness or blurred vision stage during the entire period. Usually the stramonium was administered 10 drops t.i.d. A.C., the object being to have three normal sized meals with no feedings between, an increase of one drop at each meal until the pharmacological effects were obtained. The use of stramonium for this purpose, as compared with belladonna, has been found more successful in the author's experience, possibly because of the greater hyoscyamine content and consequent antispasmodic effect. It was not necessary to carry stramonium medication to the stage of complete dryness to obtain this result, as is required with belladonna. This has been fluoroscopically confirmed on several occasions.

In the severe ulcers of long-standing, it was felt advisable, while employing the ambulant treatment, to continue the therapy outlined for a period of four to six months. The results thus far obtained have justified this prolongation of the period of treatment (Table I).

During the past year one adsorbent ant-acid powder has been employed to the exclusion of all others because of its greater effectiveness without such untoward effects as a tendency to alkalosis or hypersensitiveness to bismuth salts. During the previous three years, when the dosage of other powders was increased to the required degree, there was a tendency in some patients to alkalosis. This was counteracted by the administration of aromatic spirits of ammonia in the ante meal medication (the ammonia was converted by the hydrochloric acid of the stomach to ammonium chloride). The preparation described contains the more stable type of amonium salt, di-ammo-

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nium-hydrogen phosphate, $((NH_4)_2HPO_4 \cdot 2H_2O)$, in sufficient quantity for the same purpose. None of the patients taking this powder have required additional ammonium salts for the prevention of alkalosis.

The various adsorbents available for internal administration have been employed in an attempt to reduce the alkali or potential alkali requirements. Among these were kaolin, bismuth salts, magnesium hydroxide and oxide, aluminum hydroxide, aluminum silicate and various pharmaceutical and other combinations of the usual ant-acid chemicals used for such purposes. It has been found that a synthetic hydrated magnesium trisilicate is the most effective adsorbent for the purpose of this treatment.

Synthetic hydrated magnesium trisilicate is a light, fine powder, insoluble in water. However, distilled

TABLE I

Peptic ulcer cases

Initials	Sex	Age	Diagnosis	Confirmation by [illegible]	[illegible]	[illegible]	[illegible]	X-Ray	Gastroscopy	Previous Treatment (Diet, Lavage, etc.)	Maximum Quantity Powder in Treatment, Before and After Meals*	Results
[illegible]	M	[illegible]	[illegible]		Yes	No	Yes	Yes	No	Fifty	2 drams	Healed
[illegible]	M	[illegible]	[illegible]		"			"	"	No	2½ "	"
[illegible]	F	[illegible]	[illegible]	Yes			"	"	"	"	2½ "	"
[illegible]	M	[illegible]	[illegible]		Yes	Twice [illegible]	"	"	"	Lavage and Fifty	2½ "	"
[illegible]	M	[illegible]	[illegible]		Yes	No		"	"	[illegible]	4 "	"
[illegible]	M	[illegible]	[illegible]		"	Twice	"	"	Yes	[illegible] twice	4 "	"
[illegible]	M	[illegible]	[illegible]		Yes	No	"	"	No	"	2½ "	"
[illegible]	M	[illegible]	[illegible]		"	Twice	"	"	"	"	3 "	"
[illegible]	M	[illegible]	[illegible]	Yes		Yes	"	No	"	No	3½ "	"
[illegible]	M	[illegible]	[illegible]		Yes	No	"	Yes	Yes	[illegible]	4½ "	"
[illegible]	M	[illegible]	[illegible]		"	Yes	"	"	"	"	4 "	"
[illegible]	F	[illegible]	[illegible]	Yes		"		"	Yes	No	2 "	"
[illegible]	M	[illegible]	[illegible]		Yes	No	"	"	Yes	[illegible], etc.	2 "	"
[illegible]	M	[illegible]	[illegible]		"	"	"	"	No	No	2 "	"
[illegible]	F	[illegible]	[illegible]		"	"		"	Yes	[illegible] twice	2 "	"
[illegible]	M	[illegible]	[illegible]		"	"	"	"	No	" "	4 "	"
[illegible]	F	[illegible]	[illegible]		"	"	"	"	"	No	3½ "	"
[illegible]	F	[illegible]	[illegible]		"	"	"	"	"	"	2 "	"
[illegible]	F	[illegible]	[illegible]		"	"	"	"	"	Fifty	2½ "	"
[illegible]	F	[illegible]	[illegible]	Yes		Yes	"	"	"	No	4 "	Fairly return symptoms after [illegible]. Under treatment this date.
[illegible]	F	[illegible]	[illegible]	Yes		No	"	"	"	No	2 "	Healed
[illegible]	M	[illegible]	[illegible]	"		"	"	"	"	"	4½ "	"
[illegible]	F	[illegible]	[illegible]	"		"	"	"	"	"	2½ "	"
[illegible]	F	[illegible]	[illegible]	"		"	"	No	"	"	2 "	"
[illegible]	M	[illegible]	D.U. and [illegible]	"		"	"	Yes before and after	Yes [illegible] before and [illegible]	"	4 "	"
[illegible]	M	[illegible]	D.U.		Yes	No	"	Yes	Yes	Fifty, etc.	[illegible] "	"
[illegible]	F	[illegible]	Gastric and D.U.		"	"	"	"	"	Fifty and operation	1½ "	"
[illegible]	M	[illegible]	D.U.		"	No	"	"	No	Fifty, etc.	4 "	"
[illegible]	M	[illegible]	D.U.	Yes		Yes	"	"	"	No	5 "	Improved symptomatically, but not sufficient length of time for recheck.
[illegible]	M	[illegible]	D.U.	Yes	No	No	"	"	"	"	2 "	Healed

* In a variable proportion of ulcers [illegible] between meals it may be necessary for a time to give half the "meal time" dose of powder between meals and at bed time. The extra dosage can usually be terminated in 3 to 6 weeks even in severe ulcers, when the hypersecretion is controlled by before and after meal doses of powder.

water in contact with this compound acquires a slightly alkaline reaction, (pH 8.4), evidently due to the presence of traces of magnesium oxide and carbonate. It adsorbs large quantities of hydrochloric acid as shown by the following experiments:

To 1.000 gm. of the silicate was added 100 c.c. N/14 HCl. This was allowed to adsorb for 24 hours, after which the excess acid was neutralized with N/14 NaOH.

A series of tests on various batches of this chemical, based on the above procedure, gave an average adsorbent value of 81:2 c.c. N/14 HCl (or 116 c.c. N/20 HCl) for one gram of magnesium trisilicate.

The rate of adsorption of magnesium trisilicate by hydrochloric acid is shown in the following tables:

A. 0.250 gm. of silicate titrated with N/14 HCl using Brom Phenol Blue 0.04%.

Titrated after	2	minutes	= 5.0 c.c.	HCl	adsorbed
" "	5	"	= 11.0 c.c.	"	"
" "	10	"	= 13.1 c.c.	"	"
" "	30	"	= 15.5 c.c.	"	"
" "	3	hours	= 16.6 c.c.	"	"
" "	24	"	= 19.6 c.c.	"	"

B. 0.250 gm. titrated with N/14 HCl using Brom Phenol Blue 0.04%.

Titrated after	1	minute	= 5.0 c.c.
" "	2	minutes	= 7.5 c.c.
" "	5	"	= 10.8 c.c.
" "	10	"	= 12.9 c.c.
" "	20	"	= 13.4 c.c.
" "	30	"	= 15.8 c.c.
" "	3	hours	= 16.9 c.c.
" "	24	"	= 20.3 c.c.

Impurities in magnesium trisilicate such as soluble salts or free alkali must be guarded against, since this chemical has no standard of purity. In the author's use of this substance, it is analyzed for free sulphates, sodium oxide, sodium silicate, sodium hydroxide, soluble magnesium salts and heavy metals. The powder must also be fine enough to pass through a 200 mesh sieve for maximum efficiency.

The chemical formula of synthetic hydrated magnesium trisilicate may be expressed as the ratio of MgO to SiO_2. Analysis of various batches of this chemical, according to Scott (5), have given the following results:

Batch Sample	MgO (ignited)	SiO_2 (ignited)	Ratio	% Loss on Ignition
A.	17.6%	80.0%	1:3.00	21.0
B.	14.3	70.0	1:3.28	16.8
C.	15.3	78.4	1:3.40	28.2

Mutch (6) has referred to hydrated magnesium trisilicate *per se* as a very effective adsorbent for the treatment of peptic ulcer. Experiments with hydrated magnesium trisilicate, (which is not at the present time obtainable in this country in prepared form), demonstrate that the adsorption and neutralization of the pepsin-HCl is not very effective within the first ten minutes of contact. Since this fact would allow the digestion of food by the gastric enzymes, the substance administered alone is not suitable for the treatment of peptic ulcer. Furthermore, while the hydrated magnesium trisilicate is a very effective adsorbent, it is not perfect in this capacity, since its adsorption is available only up to approximately 50% of the salt. The remainder is converted to $MgCl_2$, and thus becomes a potential alkali. For this reason, a small amount of sodium bicarbonate and a larger quantity of a potential alkali, such as refined calcium carbonate, were incorporated in effective proportions to be at hand for immediate neutralization of peptic digestion, when the mixture was ingested before meals. The advantages of this powder containing diammonium hydrogen phosphate, sodium bicarbonate, calcium carbonate and hydrated magnesium trisilicate were readily apparent.

This powder has been employed in cases of recurrent peptic ulcer subsequent to operation, in cases with primary active hemorrhage, in recurrent cases, in previously untreated peptic ulcers, as well as in recurrent cases, treated by other physicians and myself. Only two of this series was treated with Larostidin (La Roche) without results. These responded well to the method described.

All diagnoses were definitely confirmed by operation or X-ray previous to installation of the treatment, and to the present time all have shown responses of a gratifying type. The results are given as a preliminary report so that others may avail themselves of the data.

CONCLUSION

An outline is given of a method for the treatment of peptic ulcer, based on findings concerning gastric digestion which have been previously reported. Only those cases treated during the past year with the alkali adsorbent powder*, of which a description is given, are included in this series.
tion is given, are included in this series.

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*Manufactured for the author by the Standard Chemicals, Incorporated, Baltimore, Maryland.

The Cholesterol Problem*

By

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WE are indebted to Bridges (1) for a more complete table containing the cholesterol content of various foods. It is now not difficult to prescribe a diet low in cholesterol. Those foods poor in cholesterol are breadstuffs, cereals, egg white, low fat fish, fruits, lean meats, skim milk, syrups and vegetables. Those excessively high are the solid internal organs, liver, kidney, sweetbreads, etc., egg yolk and caviar.

It is to be noted that fruits and vegetables contain some cholesterol and the only food in the list that is entirely free from it is egg white. Therefore, there is no danger in giving too little cholesterol in prescribing a diet for adults who clinically require such a regimen. Of course, the growing child requires a diet rich in cholesterol.

A review of the articles on this subject in the Transactions of the American Gastro-enterological Association for 1936 discloses that a great deal of confusion exists in evaluating the blood and bile cholesterol content. Wilkinson (2) observes that the level of blood cholesterol is affected by variations in the function of the pituitary, thyroid, gonads, pancreas and adrenals. Hyperthyroidism causes a decrease in blood cholesterol values while in hypothyroidism the values are increased. The discussion on the treatment of Chronic Hepatitis with jaundice reveals that no clear cut method has as yet been established.

The recent meeting of the American College of Physicians with a program largely devoted to cardiology contained no mention of this subject. The cardiologists appear to adhere to the theory of intravascular tension as the etiologic factor in the production of arteriosclerosis, and do not consider the lipoid deposit theory.

Elliott and Nuzum's study (3) on the "Cholesterol Content of Whole Blood in Patients with Arterial Hypertension" is of extreme interest. They state "Uncomplicated arterial hypertension is not accompanied by hypercholesteremia." "Higher values for cholesterol are found more frequently among underweight than among obese persons." Is it not possible that the cholesterol may be deposited in the tissues and not appear to excess in the blood plasma of the obese individuals? I suggested to Nuzum to subject a group to the administration of thyroid and iodide with periodic blood analyses to determine whether these lipoid solvents might release the bound cholesterol and cause larger blood plasma content.

The recent article by Jacobi (11) is a good illustration of the manner in which cholesterol deposited in the body tissues, may be released by a resolving agent. He found that cases of ulcerative lesions of the extremities due to peripheral arterial disease, were found to have a subnormal or low normal blood cholesterol. After a course of treatment with two per cent sodium iodide intravenously, the blood cholesterol showed a gradual and marked rise.

Wilder's masterly review (4) on "Diseases of Metabolism and Nutrition" shows considerable divergence of opinion among the investigators of the cholesterol factor, particularly in diabetes. Geyelin (5), Sansum (6), Adlersberg (7), Rabinowitch (8), and others are all convinced of the desirability of the high carbohydrate and low fat diet in diabetes. Wilder's final conclusion is in favor of the more liberal use of fat, and he believes his patients get along as well as those whose diets are restricted in fat content.

In the midst of all this confusion we are justified in employing our clinical judgment rather than to rely upon uncertain and misleading blood analyses. Clinically it is not a difficult problem to determine the group of patients we should subject to a dietary of low cholesterol content.

Individuals of this type, endowed with poor cholesterol metabolism have a tendency to develop *obesity, gall stones, athero-sclerosis, degenerative arthritis,* and *cataract.*

I have reviewed old case records in my files and find many such life histories. A few case reports are presented with full appreciation of the fact that one might become too enthusiastic in the evaluation of therapeutic procedures.

CASE REPORTS

Case 1. R. D. H., male, aged 39, business executive. Came under observation in June, 1913. He had digestive disturbances that appeared to be functional in character. Finally at the age of 57 in 1931 he experienced definite pain in the chest upon exertion, characteristic of angina pectoris. The pains were immediately relieved by the administration of nitroglycerin (spirits glonoin) on the tongue. He was seen in consultation with Dr. Oliver Abel, Jr., in November, 1931. His basal metabolic rate was well within the normal limits. Electro-cardiograph report was as follows: P. R. interval = 0.12 sec. 'T' waves upright in lead I. Diphasic in leads II and III. Diagnosis: Myocarditis; right axial deviation. His kidney function was good. He had a slow pulse and his skin was dry. He had a definite pruritus ani, brittle nails, and suffered a great deal from day drowsiness and fatigue. He was put on Sansum's alkaline-ash diet, being allowed four glasses of milk a day; the balance of the diet made up of cereals, bread, butter, fruits, and vegetables—in fact, quite a low cholesterol diet. He was given one grain dessicated thyroid daily. He reported from time to time and at the end of one year found that he could exercise without any further pain, had no weight loss and was in a good state of nutrition; suffered no longer from fatigue, continued his work and outdoor exercise. At the end of another year he was again checked up and we found that after discontinuing the thyroid medication he again suffered from fatigue. The dosage has been continued regularly since that time. He was last seen in January, 1937, in splendid physical condition and has never had any return of his anginal pains, six years after the initial attack of angina pectoris.

*From the Soper-Mills Clinic, St. Louis, Mo.
Submitted June 9, 1937.

Case 2. F. L. S., female, aged 65. Came under observation in 1926. Referred by Dr. W. A. Shoemaker for detached retina. Her gastro-intestinal symptoms were functional in character and responded very well to dietetic treatment. In June, 1931, at the age of 69, she developed anginal pains following exertion which were controlled by spirits glonoin in drop dosage on the tongue. In 1933 she had quite severe attacks of nocturnal pain so was put on one grain dessicated thyroid because of extreme fatigue and dry skin, although the basal rate was normal. She was seen in consultation with Dr. Oliver Abel, Jr. Electrocardiograph report was as follows: P. R. Interval = 0.16 sec. 'T' waves upright in leads I and II. Inverted lead III. Diagnosis: Left axis deviation. She was advised to limit her activities and given both thyroid and iodide of sodium, and a low cholesterol diet. The nocturnal attacks became less severe but she continued to have substernal pain upon exertion, always relieved by nitroglycerin. In January, 1934, she showed considerable degree of improvement but was not faithful to her diet and continued to be too active socially. She remained in this condition until April 9, 1936, when she experienced a severe attack of *Coronary Thrombosis*—she was sent to St. Lukes Hospital and was in a precarious condition for months. The attack was quite typical, accompanied by fever and pain, no decompensation. Since leaving the hospital she has adhered strictly to her diet and continued the use of thyroid and iodide and has resumed her usual social activities, and has not had to resort to the use of nitroglycerin which she had used for six years prior to the attack of coronary occlusion.

Case 3. C. M. S., male, aged 39. Was seen in consultation with Dr. C. E. Barnett at the Deaconess Hospital October 27, 1936. Jaundice was very definite and a tentative diagnosis of carcinoma of the pancreas was made at the hospital because of the intensive jaundice of painless onset. He was placed on small doses of magnesium sulphate every morning and a low cholesterol diet. His jaundice disappeared completely by the 4th of December. He continued to improve steadily. Cholecystogram disclosed the presence of gall stones, but his general condition is so good that he decided to postpone the operation which was advised. He continues to adhere to a strict low cholesterol diet.

Case 4. F. R. T., female, aged 58. Came under observation in November, 1921. Blood pressure 150/70. Referred by Drs. Meyer Wiener and B. Y. Alvis who found that the eyes showed some areas of retinal hemorrhage. Diagnosis of chronic interstitial nephritis was made. She was placed on a low protein diet and foci of infection corrected about the teeth and rectum. Her eye history presented by Dr. Alvis is as follows: "Her vision was normal in each eye until in 1921 when the vision of the right eye became impaired due to the presence of hemorrhage in the retina. This eye continued to a hemorrhagic glaucoma until it became so painful that it had to be enucleated in 1924. In 1926 a chronic glaucoma developed in the left eye which was controlled by miotics for some months. In November, 1926, a trephining was done on this eye followed by a good recovery; return of normal tension, vision being normal. In 1930 there was a recurrence of the glaucoma but this was controlled by the use of Pilocarpine and Eserine. In 1931 she suffered a mild deep infection which cleared up immediately on the administration of typhoid intravenously. In November, 1932, it was noted there was a clouding of the lens of the left eye with the vision reduced to 15/25 with best correction. This clouding of the lens has progressed very slowly. In February, 1935, it was noted that the lens was quite dense in the center and the vision was reduced to 15/200 and the sight remained at that level until June 20, 1935, when she suddenly noted an abrupt diminution of her vision. With dilated pupils, the lens was sufficiently clear so that the fundus could be seen, and it was observed the disc was blurred; veins were dilated and tortuous; there were numerous hemorrhages. The vision at that time was 7/300. Since that time there has been some improvement in the vision due to the absorption of the hemorrhages and retinal edema while the lens remains sufficiently clear to afford a fairly satisfactory view of the fundus. On February 3, 1937, the vision was 15/200 and the details of the fundus could be seen rather clearly."

She was placed on small doses of thyroid and kept under continuous observation since then. In 1932 her blood pressure was 180/100; N.P.N. -35 mg. per 100 c.c. of blood. Since the retinal hemorrhage in 1935 she has been on a diet very low in cholesterol, to which she has adhered conscientiously. Her daily dose of dessicated thyroid is two grains. Sodium Iodide is given intermittently. Her N.P.N. is now 26 mg. per 100 c.c. of blood; blood pressure 140/80. She maintains a good state of nutrition and is active for her age (74 years). Is able to read large print better than she could in 1934.

Case 5. B. H. B., male, aged 56, banker, 5 feet. 8 inches. Weight 210 lbs. Came under observation October 20, 1936. Had diabetes for 18 months. Was taking 20 units insulin daily and was on a diet of high fat content.

His blood sugar curve was as follows:

Fasting	½ hr.	1 hr.	2 hrs.	3 hrs.
126 mg.	194 mg.	201 mg.	207 mg.	189 mg.

He complained of great deal of nervousness, slept poorly and had digestive disturbances. The urine was found to contain hyalin and granular casts and approximately one per cent sugar. N.P.N. was 35 mg. per 100 c.c. of blood. Physical examination showed blood pressure 120/70; palpable arteries were definitely sclerotic; *liver was very hard a hand's breadth below the rib margins.* His basal rate was well within the normal limits. He was placed on a low cholesterol diet, gradually increasing the carbohydrates, given one grain dessicated thyroid once daily. He made steady improvement; his liver became smaller and within 60 days was barely palpable at the rib margins. He now discontinued his insulin and continued to lose weight. A check-up on March 1, 1937, revealed fasting blood sugar 115 mg. per 100 c.c. of blood; N.P.N. -24 mg. per 100 c.c. of blood. Weight 170 lbs. General condition excellent. 24 hour specimen of urine free from sugar.

Following the suggestive work of Lockie and Hubbard (9) I have achieved excellent clinical results in the treatment of a group of 6 patients suffering from *Gout.* In the acute stage, Colchicine was given followed by low cholesterol diet and the administration of thyroid and iodide. No patient has had a recurrence of the acute symptoms. This method is far better than the use of the dangerous drug Cincophen so much in vogue in the treatment of gout.

Dr. J. Albert Key, Professor of Orthopedic Surgery in the Washington University School of Medicine has had quite a large experience in the treatment of degenerative arthritis. Quoting from his paper on the subject (not yet published) "the treatment consisted of a low fat diet supplemented by thyroid medication." "We found that our patients with degenerative arthritis do better than have similar patients in the past under any other form of treatment which we have used." "We feel that we are able to prevent the progress of the disease in cases in which it is definitely present and to prevent its development in the type of individual in whom it is to be expected."

Of course, there exists spontaneous arrest of cataract as well as unexpected improvement in heart dis-

ease regardless of diet or other forms of therapy. Dr. Paul D. White (10) in his report "A New Record of Longevity After Coronary Thrombosis" advised and achieved weight reduction in this patient.

The cases that I report are representative of the various conditions in which low cholesterol diet and the administration of thyroid and iodide have been useful. A proper appraisal of the method comes from retrospect and consideration of the general results secured in patients treated prior to the employment of this method.

The larger number of patients who have been benefitted by this treatment include those who in middle life begin to develop symptoms of degenerative arthritis, gall bladder disease, and arteriosclerosis.

It looms large on the Horizon of Preventive Medicine.

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Hypoglycemia

A Study of 404 Patients Who Had No Insulin and Had This Common Finding*

By

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HISTORY

IN spite of the importance of hypoglycemia there has been but little about it in the medical literature until the past ten years. Since then, although the reports have been numerous, the main interest has been centered in one phase of the subject, hyperinsulinism. In most of the reports this condition has been taken for granted as an explanation of a symptom complex, the nature of which is yet to be proved and for which a state of hyperinsulinism could at most be postulated as its immediate cause.

The study to be reported was undertaken since there did not seem to be an adequate investigation of a large group of cases covering the broad field of hypoglycemia. It seemed unlikely to us that the label hyperinsulinism was sufficiently conclusive and that Camidge's conclusions were correct interpretations of the nature of the condition.

To this end we have reviewed the available histories of the patients in the Johns Hopkins Hospital in whom hypoglycemia was discovered. It has been our aim to determine the frequency with which hypoglycemia was found and to correlate this finding with diagnosis, symptoms, and as many abnormal characteristics as would seem feasible and logical.

We have found that a low blood sugar was associated with a number of organic pathologic conditions and furthermore that it is also at times low in association with a condition which we can now best classify as an abnormal functional state. Later in the article we attempt to describe the hypoglycemia found in psychoneurotic individuals and which we do not feel is responsible for their symptoms since these symptoms remain during shifts of the blood sugar concentration to normal levels and in contrast to them there is a small group whose low level of the blood sugar seems definitely connected with their symptoms. These patients are always temporarily relieved of their unpleasant symptoms by partaking of carbohydrate, preferably in the form of sugar.

Porges (1) in 1910 noted that individuals suffering from Addison's disease frequently had a low concentration of sugar in their blood. Carrying on the suggestion stimulated by this finding he was able to show that when dogs were adrenalectomized their blood sugar also diminished. In 1912 in his book "The Pituitary Body," Cushing (2) mentions the finding of a low blood sugar in one of his patients who had a pituitary tumor. Another observation on hypoglycemia was made by Joslin (3) in 1921; in three diabetics who had been undergoing the Allen Treatment he found an abnormally low concentration of blood sugar.

The first references to a state of hyperinsulinism were made by Seale Harris (4) and by Ross and Josephs (5) who in 1924 independently reported cases of spontaneous or idiopathic hypoglycemia. Since then Harris has followed up the subject and has reported a number of additional cases. He recently reviewed this phase of hypoglycemia (6).

Three years later, Wilder, Allen, Powers and Robertson (7) published a detailed report of a patient with carcinoma of the islets of Langerhans in whom the blood sugar was very low. They state that extracts from the tumor and from the metastases in the liver contained increased amounts of insulin.

Several additional cases have been reported since. Phillips (8) described the pancreas of a man who died

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of nephritis in whom there was a low concentration of blood sugar. At section he states that the islets of Langerhans were definitely increased in diameter throughout the gland.

The first report of a large number of cases was made by Cammidge (9) in 1930. His series includes two hundred patients of whom he said that 47 per cent had some infection in the upper intestinal tract. He did not give his criteria for diagnosis. He also stated that there was an hereditary hypoglycemic factor in 35 per cent and that acetonuria was found in 25 per cent. He asserts that most of the cases could not be cured until the upper intestinal infection had been successfully treated. He did not mention technic of therapeusis.

There are two splendid critical reviews on the subject of hypoglycemia, one by Sigwald (10) in 1932 who also reports some cases of his own and the other by Wauchape (11) in 1933. As they both have fully covered the available reports on the subject, a further discussion of it here would be superfluous.

TABLE D-I

Showing the total number of cases (404) arranged according to organic, nonorganic, and unknown basis for hypoglycemias. Also arranged to show the relationship of symptoms to diagnosis

TOTAL NUMBER OF CASES WITH	TYPE OF SYMPTOMS		3. No symptoms
1. Organic Basis	1. Definite	2. Suggestive	
Pancreatic Tumor	1	0	0
Liver Disease	12	7	24
Addison's Disease	5	11	0
Hyperthyroidism	0	5	11
Low Basal Metabolic Rate	1	6	8
Pregnancy	1	5	6
Dwarfism	0	1	0
Simmond's Disease	0	1	0
Paraxysmal Hypertension	1	0	0
Myocardial Insufficiency	1	1	11
Severe Infections	0	0	11
Total	22	37	71
2. Nonorganic Basis			
General	0	3	54
Psychoneurosis	0	22	34
Functional Hypoglycemia with symptoms	10	0	0
Renal Glycosuria	0	3	30
Epilepsy	4	3	3
Arthritis { Infectious / Metabolic	0	0	27
Obesity	0	0	7
Gastro-Intestinal	0	1	18
Total	14	32	173
3. Unknown Basis			
Blood	0	4	8
Narcolepsy	0	1	0
Undiagnosed	0	2	1
Neoplasm	0	1	8
Neurological	0	3	13
Hypertension	0	2	12
Total	0	13	42

INTRODUCTION

Before presenting our data and discussing their possible significance we wish to give our definition of hypoglycemia and, what is equally important, that of a normal glucose tolerance test.

From the numerous reports in the literature it may be accepted that the normal fasting blood sugar is generally about 100 mg. per cent, but it may vary from 80 to 110 mg. per cent. These limits are somewhat conservative in the opinion of certain investigators, but it is our belief that blood sugar estimations below 80 mg. per cent represent an unusual condition if not an actual abnormality.

Considerable investigative work has been devoted to the purpose of establishing the limits of a normal glucose tolerance test. Many of the earlier articles reported upon too small a number of cases to be convincing. Later reports have eminated from the Scandinavian countries which do carry conviction. From these reports it seems settled that after the ingestion of 75 to 125 grams of glucose the blood sugar rises rapidly from a control level of about 100 to 140 or 180 mg. per cent and during the period of the next two or three hours drops back to the fasting level. During the descent it frequently drops below the control level, but if it drops below 70 to 65 mg. per cent it again represents an unusual if not abnormal reaction.

METHODS

All of the laboratory findings to be presented on the test cases were made in the biochemical laboratories of the medical department of the Johns Hopkins Hospital. Recognized standard methods were used for the various determinations. Specimens of blood were in the great preponderance of cases obtained from the vein. But few of the blood sugars were estimated from the capillary blood; those that were done in that manner were usually made in conjunction with venous blood in especially selected cases such as Addison's disease, myxoedema and parenchymatous liver disease.

The urine determinations were made in the customary manner by medical house officers or fourth year students and in general were carefully and accurately performed and interpreted.

CONTROL

The control cases represent one hundred patients studied in the office laboratory of the senior author. The laboratory investigations were made in accordance with standard technic and performed by an experienced technician. Capillary blood was used for the glucose tolerance tests.

The patients represent a cross section of the usual private practice and as some investigative work was being done on cases of hypertrophic arthritis, a good proportion of these cases are among those reported. The control patients selected were those whom fasting blood sugar, a glucose tolerance test and a basal

metabolic rate had been determined on each. In none of these cases was the fasting blood sugar below 80 mg. per cent.

The glucose tolerance curves of 50 cases showed a slightly lowered tolerance and only one dropped below seventy. There was one case with suggestive symptoms of hypoglycemia in which the curve remained flat and dropped below 70. In three patients with otherwise normal glucose tolerance curves the blood sugar dropped below 70 mg. per cent during the test. We were unable to find any relationship between the type of curve and the basal metabolic rate.

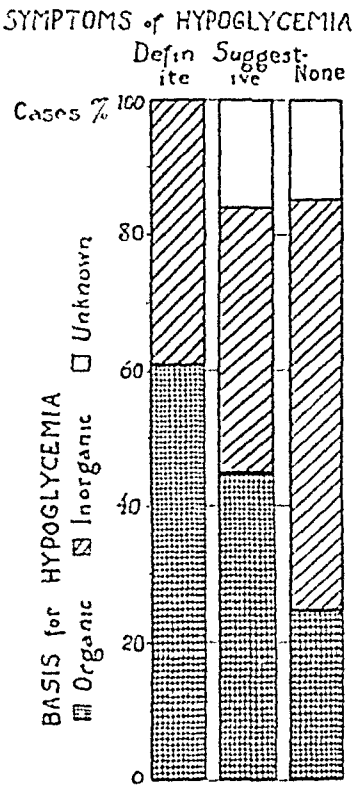


Fig. 1. Shows the percentage of the total number of cases with definite symptoms, suggestive symptoms and no symptoms whose hypoglycemia was the result of organic, inorganic or unknown etiology.

TEST CASES

There were 63 patients whose fasting blood sugar was above 80 mg. per cent but which dropped below 70 mg. per cent during the glucose tolerance test. There were 63 patients whose fasting blood sugar was between 71 and 79. The large group includes 278 patients who were found to have at least one fasting sugar below 70 mg. per cent. In 54 of them there were one or more tests made, when the fasting blood sugar was below 50 mg. per cent.

The lowest reported is 4 mg. per cent, the exactness of this reading is of course questionable, but was repeatedly obtained from the same blood specimen. This was determined on the fasting blood of a patient who was in a coma. He was given glucose intravenously, as a result of which his blood sugar level went above 200 mg. per cent and restored him to a temporary state of well being. It was proved at autopsy that he had an adenoma of the pancreas.

The next lowest determination 15 mg. per cent (repeated) was found in a blood specimen removed from a man who was in deep coma as a result of what was apparently an unwise, if not excessive use, of hard liquor.

Age and Sex: The roster of patients included persons of all ages, the youngest a few months, the oldest aged. The largest representation was between twenty years and fifty years and was more or less equally distributed among the decades.

SYMPTOMS

While the histories were abstracted notes were made for guidance in the determination of which symptom group the patient was to be classified. They are as follows:

1. Symptoms of hypoglycemia: The patients in this group were selected when there seemed to be a direct relationship between symptoms and hypoglycemia. Either as found in a fasting blood specimen or in specimens taken during the day or during the progress of a glucose tolerance test.

Weakness, nervousness, recurrent early morning headache, anxiety, trembling, lassitude, sweating, inability to concentrate before meals, marked hunger were considered significant symptoms. Some of the patients become semi-comatose and even developed convulsive attacks. It was generally noted that if hypoglycemia was the cause of these symptoms, they were quickly dissipated by food. This group contains 36 patients.

The number of patients actually observed having spontaneous hypoglycemia symptoms during the course of a day, normal for them, was small. A patient with adenoma of the pancreas, one with myxoedema, several with Addison's disease, three during severe acute alcoholism, and ten with symptomatic functional hypoglycemia of unknown etiology.

2. Symptoms suggestive of hypoglycemia: There were a number of patients whose symptoms were suggestive of hypoglycemia but which we were unable to recognize as directly related to their blood sugar concentration. It is probable that some of them were the result of hypoglycemia and others were merely expressions of psychoneurosis connected with a lowered blood sugar which was above the symptom producing level. There are 82 cases in this group.

3. No symptoms suggestive of hypoglycemia: In this group of 286 we have placed the great bulk of the patients. It may be that some of those diagnosed as psychoneurotics should have been placed in Group II but we feel that the potential errors in both groups will more or less balance.

PHYSICAL EXAMINATION

Obesity was noted in 22 of the patients, 17 of whom were found to have blood sugar levels which placed them in the second group. Malnutrition was evident in 29 patients and again was most in evidence in those patients with a low fasting blood sugar. The liver was definitely enlarged in 16 nonjaundiced patients and the spleen in 8. Jaundice was noted in 16 patients in some of whom the liver was thought to be decreased in size.

DIAGNOSIS

It is noteworthy that an hypoglycemia was found to

TABLE D-II

Showing the total number of cases arranged in relation to three fasting blood sugar levels and further arranged, as in Table D-I, according to the organic, inorganic and unknown basis for the hypoglycemia in these 278 cases. Also arranged to show the relationship of symptoms to diagnosis and to fasting blood sugar levels

TOTAL NUMBER OF CASES WITH	TYPE OF SYMPTOMS AND FASTING BLOOD SUGAR BETWEEN								
	0-49			50-59			60-70		
1. Organic Basis	Def.	Sug.	None	Def.	Sug.	None	Def.	Sug.	None
Pancreatic Tumor	1	0	0	0	0	0	0	0	0
Liver Disease	7	0	1	1	3	3	2	3	15
Addison's Disease	1	3	0	2	3	0	2	5	0
Hyperthyroidism	0	0	0	0	1	1	0	4	4
Low Basal Metabolic Rate	0	0	0	0	1	3	1	5	3
Pregnancy	0	2	0	0	2	3	1	1	3
Dwarfism	0	0	0	0	0	0	0	1	0
Simmond's Disease	0	1	0	0	0	0	0	0	0
Paraxysmal Hypertension	0	0	0	0	0	0	1	0	0
Myocardial Insufficiency	0	1	1	0	0	1	0	1	4
Severe Infection	0	0	0	0	0	5	0	0	3
Total	9	7	2	3	10	16	7	20	32
2. Inorganic Basis									
General	0	0	1	0	1	5	0	2	21
Psychoneurosis	0	0	1	0	0	2	0	9	25
Functional Hypoglycemia with symptoms	1	0	0	1	0	0	5	0	0
Renal Glycosuria	0	0	0	0	0	2	0	3	17
Epilepsy	0	0	0	0	0	0	4	4	1
Arthritis { Infectious	0	0	0	0	0	4	0	0	10
Arthritis { Metabolic									
Obesity	0	0	0	0	0	1	0	0	5
Gastro-Intestinal	0	0	1	0	1	2	0	0	4
Total	1	0	3	1	2	16	9	18	83
3. Unknown Basis									
Blood	0	0	1	0	0	0	0	2	3
Narcolepsy	0	0	0	0	0	0	0	0	0
Undiagnosed	0	1	1	0	0	0	0	1	0
Neoplasm	0	0	0	0	0	0	0	1	4
Neurological	0	0	0	0	2	1	0	1	4
Hypertension	0	0	0	0	1	2	0	2	11
Total	0	1	2	0	3	3	0	7	22

be associated with a large number of ailments. The complete data are given in the tables and only the more significant findings will be mentioned here.

The largest group of cases was placed under the diagnosis designated as General, which included 35 entities such as: dermatitis, flat feet, ureteral stricture, chronic bronchitis, furunculosis, benign prostatic hypertrophy, inguinal hernia, allergic conditions, etc., other more specific diagnosis were: psychoneurosis, renal glycosuria, hypertension, myocardial insufficiency, neurological disorders, Addison's disease, arthritis, hyperthyroidism, low basal metabolic rate, parenchymatitis, liver disorders, gastro-intestinal disease, blood diseases and others less frequently noted.

There were 33 patients with renal glycosuria, a striking proportion of whom had a psychoneurotic leaning.

We were interested in 43 cases of liver disorders, among which carcinoma, arsphenamine induced hepatitis, alcoholism (3 cases), cartarrhal jaundice and induced malarial infections in patients with central nervous system syphilis, all of which gave low fasting blood sugar readings. On a case of cirrhosis, which was verified at necropsy, and which was clinically thought to be due to chronic alcoholism, an epinephrine test was done, it failed to show the usual rise in blood sugar.

Among the patients, three suffering from the effects of sustained use of alcohol, were especially interesting. The first, a man, was brought into the accident ward in a coma. His extremities were rigid, his skin moist, his blood sugar 15 mg. per cent. Dr. Tom Brown, a house officer, saw him, and was so impressed with the clinical picture that he made the diagnosis on the other two cases. In these patients two features are of importance, one the abstinence from food, and second the possible glycogenolytic influence of alcohol on the liver.

For the sake of thoroughness we add the specific diagnosis of the cases grouped under the heading "neurological." It is not deemed of importance to go into a detailed description of each as they were not particularly interesting from the point of view of sugar metabolism. The neurological diagnoses include multiple sclerosis, 3 cases; trigeminal neuritis; Parkinsonism; brain tumor, 3 cases including hypophysial tumor; myasthenias gravis, 3 cases; progressive muscular dystrophy; familial periodic paralysis; brain abscess, 2 cases; and severe head injury.

There were 5 cases of myxoedema; from a physiological view point hypothyroidism would seem to be one of the factors causing hypoglycemia.

Arthritis has frequently been reported to be associated with a low sugar tolerance. We report 27 patients in whom the fasting blood sugar was low or in whom the glucose tolerance test shows a low blood sugar at some time.

COURSE

On a number of the patients blood sugar tests were repeated at long intervals of time. They frequently varied from low to normal and it has been impossible, except in rare instances, to correlate this with a change in the condition of the patient.

Addison's disease offers an interesting illustration of symptomatic improvement in association with rise in blood sugar. It was repeatedly noted that epinephine would temporarily raise the blood sugar and relieve symptoms. Successful treatment with cortin would also cause a rise in blood sugar. Patients recovering from severe parenchymal liver disease also showed an increase in blood sugar in association with improvement.

We could find no correlation between hypoglycemia and death rate.

GLUCOSE TOLERANCE

One of the tests which has held our sustained interest in this investigation is the glucose tolerance. On analysis one is enabled to divide the results into seven main groups.

1. The normal curve starting about 90 to 100 mg. per cent, not going higher than 170 and returning to the starting level by three hours. At some time a low fasting blood sugar was found in each of the patients.

2. The low curve starting below 70 rarely going higher than 110 to 115 and returning to, or somewhat

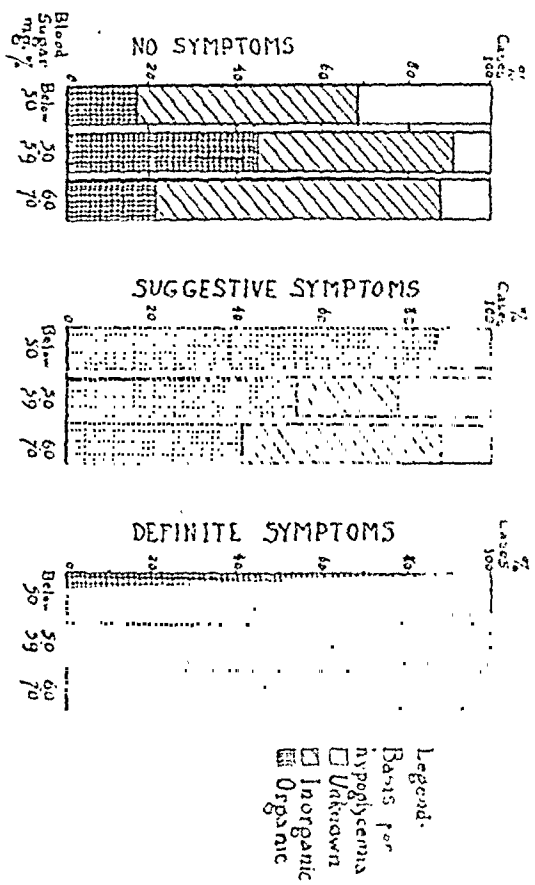


Fig. 2. Cases having no symptoms, suggestive symptoms and definite symptoms are arranged according to their respective fasting blood sugar levels and the percentage of cases having organic, inorganic and unknown etiology are shown in relation to symptoms and fasting blood sugar levels.

below, the starting level by three hours.

3. The normal rise with hypoglycemia drop. Starting about normal, reaching the usual elevation, and rapidly dropping below 65 mg. per cent.

4. The low starting diabetic curve which does not return to normal in three hours.

5. The normal starting, high rising curve going above 200 mg. per cent and rapidly descending below 65 mg. per cent.

6. The normal starting diabetic curve found in association with one or more low fasting blood sugar concentrations.

7. The flat curve sometimes remaining constantly at a low level, and at times just about 90 to 100 mg. per cent throughout.

For ease in tabulation curves four and six have been grouped together. Study of the cases to show

TABLE D-III

Showing the relation between symptoms and type of glucose tolerance curve

Type of Curve	1	2	3	4 & 6	5	7
Patients with Definite Symptoms	1	5	5	2	1	9
Patients with Suggestive Symptoms	4	8	15	1	2	2
Patients with No Symptoms	5	19	50	7	5	3

the relation of fasting blood sugar to glucose tolerance brings out the fact that normal curves are rare, twelve in number. It demonstrates that the low starting, but slightly rising curve (type 2) is the second most common, and that the one starting from a normal level, rising moderately, and dropping below 65 mg. per cent (type 3) occurred in about 50 per cent of the cases. It occurs most frequently in association with normal fasting blood sugar. The diabetic curves are not very common. Curve 5, i.e. that starting at a normal level, rising above 200 mg. per cent, and dropping below 60 was found to be associated with a constant normal fasting sugar.

The Relation of Glucose Tolerance Curve to Diagnosis: The distribution of the type of glucose tolerance curve among the various diagnoses had a general spread. There were one or more typical curves found in association with whatever diagnostic group the tests were performed. Furthermore where a sufficient number were done on the patients of any diagnostic group it was noted that three or more types of curve occurred. If the number of patients was sufficiently large, all types were to be expected.

BASAL METABOLIC RATE

The basal metabolic rate was determined on 141 patients, on 60 of them it was found to be between +10 and —10 per cent, on 48 of them below —10 per cent, on the remaining 33 it was above +10. It was very low, below —30 on 6 patients, and very high above +30 on 12. It is, therefore, evident that hypoglycemia is found associated with wide variations in basal metabolic rates.

There were 54 of the hypoglycemic patients on whom both basal metabolic rates and glucose tolerance tests were done. No correlation with symptoms was noted.

The relation of basal metabolic rates to blood cholesterol in the presence of hypoglycemia was studied in only 13 cases. In 2 cases of myxoedema and 1 of Addison's disease there was a low basal rate in conjunction with an elevated blood cholesterol. There was one undiagnosed endocrinopathy with a normal basal rate and a high cholesterol. In 3 cases of Addison's disease

there was a low basal and a low cholesterol. In 3 cases of Addison's disease there was a low cholesterol and a normal basal rate. The other 4 cases of Addison's disease had a low basal rate and a normal blood cholesterol. Consequently a relationship seems unlikely.

VARIOUS ANALYSES

There was no correlation between hypoglycemia and the blood pressure, Wassermann reaction, blood cell counts, non protein nitrogen, blood uric acid, gastric analysis, phenosulphonophthalein test, serum calcium, phosphorus, bicarbonates, cholesterol and proteins.

Epinephine Tests: Epinephine tests were carried out on 9 patients, on some of them repeatedly, in only one instance, a case of cirrhosis, did a normal response fail to occur.

PHYSIOLOGY

The fundamental approach to an understanding of the several bases of hypoglycemia is a physiological one. That our discussion may be presented in a setting that will give the widest scope to the significance of the data outlined we take the liberty of reviewing a few of the recent and simple facts and theories of carbohydrate metabolism.

It is substantially accepted that after glucose is absorbed into the blood stream of a normal individual, it is stored in the liver as glycogen, held in the muscles for energy requirements, excreted, at times, in the urine, or perhaps stored for a time in the intercellular fluid. It is also apparently true that any other hexose than glucose such as fructose, galactose and levulose, is changed into glucose by the liver before it becomes acceptable for use in furnishing local energy to muscles.

In the fasting stage we may consider the liver to be the storage organ for glucose. The factors which control the distribution of glucose to the body center in this gland. It is logical if glucose is not available for storage or if the liver does not store it, either as a result of external influences or from intrinsic parenchymatous pathological processes, that there should be changes in the blood sugar content. It is likewise logical that this should be the result of an exaggerated or uncompensated increase in the strength of those factors which promote glycogenolysis. If the organism is deprived of glucose and other glucose producing food, the glycogen storage in the liver is markedly diminished. It has been noted that protracted fastings in man will lower the blood sugar level.

All of the stages in the formation and breakdown of glycogen are not understood, but it is possible to postulate conditions which will interfere with the removal of glucose from the blood stream and its deposit as glycogen in the liver. That insulin plays an important part in this process is suspected; when it is present in sufficient amounts the normal storage of liver glycogen takes place, when it is diminished or lacking as in diabetes, a diminution of liver glycogen follows. Whether it aids in the formation of liver glycogen, is an unsettled point, but that it has an important action in inhibiting glycogenolysis, or the liberation of glucose from the liver to the blood stream is apparently proven. Consequently, when the liver is functioning within stabilizing limits, a normal secretion of insulin is associated with a normal blood sugar level, but a diminished secretion, as in diabetes, will either diminish the storage rate of glycogen and permit glucose to accumulate in the blood or fail to hold glycogenolysis in check. As the secretion of insulin is controlled by hormonal or neurogenic factors, functional states of hypersecretion are theoretically possible. That such a state occurs clinically has not been proven, although it has been postulated as an explanation for some of the reported cases of hyperinsulism with symptomatic hypoglycemia. Increased secretion is also asserted to be the result of adenoma and carcinoma of the island cells of Langerhans. The effect of an hypersecretion of insulin would be of such a nature as either to withdraw an excessive amount of glucose from the blood for glycogen storage in the liver or to further inhibit glycogenolysis. This would reduce the concentration of sugar in the blood.

Houssay's (12) observation, that the hyperglycemia in pancreatectomized animals was notably reduced after hypophisectomy opened the way for demonstrating the importance of another substance of unknown nature which assists in the maintenance of a normal blood sugar level. Apparently the pituitary gland secretes this substance and it acts directly on the liver or in combination with insulin to increase storage of glycogen or to decrease glycogenoloysis. In a pancreatectomized animal the liver, when protected from this influence is apparently able, in a degree, to compensate for the loss of insulin.

A third equally important chemical substance essential for maintaining a normal blood sugar level is epinephine, a secretion product of the adrenals. Its influence is opposed to that of insulin and acts as a brake against it. When the blood sugar drops below a certain level the adrenals are stimulated to secrete more epinephrine. This in turn acts upon the liver to cause increased production of glucose and a rise in blood sugar. When the adrenals are removed the blood sugar level drops. Addison's disease in man offers an excellent example of the effects of lowered adrenal efficiency. That the associated hypoglycemia is not due to an hypersecretion of insulin or to liver disfunction is shown by the prompt elevation of the blood sugar that follows an injection of epinephrine. It may be added that following cortin injections in these patients their blood sugar as well as cholesterol also increases.

Although there may be no discernable changes in the secretion of substances which govern carbohydrate metabolism and maintain a normal blood sugar level, there may be extreme changes noted in it as a result of parenchymatous liver change. The investigations of Mann (13) and Banting (14) and further corroborated by Soskin (15), prove the fundamental importance of the organ in supplying glucose to the body. As could be expected from the fact that removal of the liver causes a precipitous fall in blood sugar, severe parenchymatous liver disease will, as shown in our data, bring about the same result. At this point, it may be noted that in one case of severe cirrhosis (proven post mortem) an injection of epinephine failed to produce the customary rise in blood glucose; the obvious cause being a markedly diminished glycogen store in the liver. An interesting corrolary to this has been shown in the case of Von Gierke's disease in which the glycogen storage of the liver is excessive and there is an hypoglycemia. When epinephine is injected into these patients there is no increase in blood sugar. The suggestion naturally presents itself that some other external influence must be

acting not only to increase the action of insulin in inhibiting glycogenolysis but also sufficiently strong to prevent the added increment of epinephine from stimulating that process. This might well be the hormone liberated by the hypophysis and responsible for the phenomenon noted by Houssay.

The secretion of the thyroid gland has an effect in carbohydrate metabolism which may act in two ways. First physiological, and presumably in the adrenals, and second as a toxin reacts on the liver cells. Consequently although in states of hypothyroidism an hypoglycemia is to be expected it may also be a result of liver damage by thyroxin.

DISCUSSION

In the description of the data noted in the tables we have shown a number of normal or abnormal conditions in their relation to a state of hypoglycemia. We have shown that it was found irrespective of age, sex or color. It has been found within wide variations of basal metabolic rates. It is associated with extreme quantitative changes of the blood count, blood pressure, N.P.N., uric acid, phenolsulphonphthalein excretion, gastric acidity, phosphates, proteins and cholesterol. It has been noted in acidosis and it is associated with almost any type of glucose tolerance curve. We have not found a significant change in serum calcium to be concomitant with it.

It is associated with a large number of pathological conditions some of which are responsible for the lowered blood sugar by interfering with the organs, or nerves or hormones which control the normal carbohydrate metabolism. Cases falling in this group might be said to have an organic basis for their hypoglycemia. We have also found a number of pathological states in which we cannot recognize any conditions which cause a lowering of blood sugar. Exception might be made to the inclusion of cases of renal glycosuria in this group; nevertheless, we cannot recognize any basis for the glycosuria.

There is a number of patients with blood dyscrasia, neoplasm, neurological states (including three cases of myasthenia gravis), hypertension, and undiagnosed conditions the nature of whose etiological association with hypoglycemia we do not understand. These are listed as of unsettled etiology.

We have, in Table D-I, classified our patients in three groups representing the etiological basis for their hypoglycemia and find that the distribution is as follows: 1. Organic basis: 32.2 per cent; 2. No organic basis: 54.2 per cent; 3. Unsettled basis: 13.6 per cent; it is especially noted that only about a third of them had a recognizable organic basis for their abnormality.

This table also divides the cases according to their symptoms, i.e. whether they had definite or suggestive or no symptoms of hypoglycemia; from the Table D-I and Figure 1 the following summary may be deduced:

1. Definite symptoms were noted in only 8.9 per cent of all the patients whereas those with suggestive and definite symptoms were calculated as 28.8 per cent of the total number.

2. There were no symptoms of hypoglycemia in 71.2 per cent of the patients.

3. Among the patients with definite symptoms of hypoglycemia there was a recognizable organic basis in 60 per cent of the cases.

4. Among the patients with symptoms suggestive of hypoglycemia there was a recognizable organic basis in 43 per cent of the cases.

5. In the patients with no symptoms of hypoglycemia there was a recognizable organic basis for the condition in 24 per cent of the cases.

It is furthermore shown in Table I that in each of the diagnostic grouping with the exception of our diagnostic group called true functional hypoglycemia with symptoms, and Addison's disease, there are more patients having no symptoms than with positive or suggestive symptoms. This would naturally suggest to the reader the thought that those having positive or suggestive symptoms had a lower blood sugar than those who had no symptoms.

The data relative to this sensible query are shown in Table D-II which includes 278 cases whose fasting blood sugar was below 70 mg. per cent. They are classified, as in Table D-I, according to the organic or non organic or unknown basis for their hypoglycemia, and these cases are further yet subdivided in regard to the presence or absence of symptoms of hypoglycemia. The other 126 cases which are not included were either in the 70's or were low only during the course of a glucose tolerance test.

When classified according to their etiology as described above the distribution is as follows: 1. Organic basis 38.3 per cent; 2. Non organic basis 48.2 per cent; 3. Unsettled basis 13.5 per cent. These figures are close enough to those of the entire group (Table D-I) to be significant. This is especially so when we compare the percentage of the smaller groups having positive or suggestive symptoms, 28.8 per cent, to a similar percentage of 27.2 when the total number of cases was calculated.

The most important data in Table D-II was obtained by dividing the cases into three parts arranged according to their lowest fasting blood sugar; first those below 50 mg. per cent, 25 cases; second, between 50 and 59 mg. per cent, 54 cases; third, between 60 and 70 mg. per cent 197 cases.

The data has been summarized in Figure 2 to show the relation of symptoms and etiology to fasting blood sugar levels. Where definite symptoms were noted an organic basis was also present in the vast majority of cases whose blood sugar dropped below 50 mg. per cent. When the fasting blood sugar was in the fifties and the sixties there was a smaller number of cases with definite symptoms. To a striking degree this same relationship was noted in those cases who had symptoms suggestive of hypoglycemia. When the fasting blood sugar is in the sixties there is less than a 50 per cent chance that the patients having definite or suggestive symptoms will also have an organic basis for their hypoglycemia. A marked contrast is to be noted in that large group of patients with no symptoms. There a very much smaller number of cases having an organic basis was noted. It is equally important to realize that 70 per cent of all the patients with a fasting blood sugar in the sixties had no symptoms of hypoglycemia and that only 23 per cent of these had an organic basis.

Most of the cases of functional hypoglycemia with definite symptoms in this study were found to have fasting blood sugars in the higher ranges. Their fasting blood sugars were 60, 81, 65, 57, 45, 70, 60, 78, 90, 68 mg. per cent. On 6 of those cases symptoms of hypoglycemia were apparent during a glucose toler-

ance test. These cases seem to have symptoms at a higher level of blood sugar than those patients who have an organic basis for their hypoglycemia.

The facts stated in the last few paragraphs must give us pause when we consider the increasingly large number of reported cases of so-called "hyperinsulinism." What is it that produces symptoms in some patients when the blood sugar level is in the 70's and in others only when a lower concentration is attained? In the first place, there seems to be no definite point below which symptoms of hypoglycemia will become clinically discernable. In the second place, it would seem that the patients with symptomatic functional hypoglycemia are hypersensitized to a lowering of the blood sugar level. Further studies may reveal some fundamental basis for this reaction.

We have found 179 patients with fasting blood sugars below 70 mg. per cent who did not have symptoms of hypoglycemia. In contrast to this, we can point to 26 patients with fasting blood sugars at 70 or above who had definite or suggestive symptoms and includes 6 of the 10 cases of symptomatic functional hypoglycemia; these patients apparently have symptoms at a higher level of blood sugar than those patients who have an organic basis for hypoglycemia, and also at a higher level than the psychoneurotic individual, who by definition has no known organic basis for his symptom complex.

To evaluate the importance of hypoglycemia in the cases of psychoneurosis is very difficult. There is in the literature considerable reference to a number of patients with hyperinsulinism, who, until this diagnosis was pinned on them were considered psychoneurotics. Then after their diets were adjusted many were reported as being markedly benefitted, or symptom free. Many of our patients had symptoms that might have been considered as suggestive of hypoglycemia. It should be noted that these symptoms were constant and that they were also present when their blood sugar was normal. It is our opinion that, in the preponderant majority of instances, the symptoms were those so common in psychoneurosis and not a result of hypoglycemia. Furthermore, as we more carefully choose our cases we shall probably find other factors which help to differentiate the symptoms of true functional symptomatic hypoglycemia from psychoneurosis with hypoglycemia.

It has been mentioned just above that 6 of our cases of functional symptomatic hypoglycemia were positively classified on the basis of a glucose tolerance test. This brings up an important question. Do the results of this test have a real significance, and are we able by them better to classify our cases of hypoglycemia?

It has been noted that this test was performed on 144 patients and their various types of response to the ingestion of large amounts of glucose are shown. In Table D-III we have arranged these types of response in relation to the patient's symptoms. It demonstrates that there is no relation between symptoms and type of response. It may be recalled that there were 286 patients with hypoglycemia in whom no symptoms were noted and from Table D-III one can deduce that 19 per cent of them were found to have an hypoglycemia only by means of the glucose tolerance test. By individually picking out the cases, we found that 21 per cent of those with definite or suggestive symptoms were recognized or proved by means of the glucose tolerance test. Of this number, 8 were recognized as having definite symptoms and constitute 22 per cent of all the cases with definite symptoms, obviously a sufficient number to give significance and importance to the test.

In the discussion of glucose tolerance tests one might ask if the extent of the fall of the blood sugar might not be an important factor and again as in the discussion of fasting blood sugar whether the presence of an organic condition responsible for the disturbed carbohydrate condition might not also be an important factor?

In 11 patients, the glucose tolerance curve at some point dropped below 49. mg. per cent and in 74 per cent of these cases there were suggestive or positive hyperglycemic symptoms. It might furthermore be stated that only 2 of these patients had discernible pathologic bases for this abnormal reaction. In 17 instances the glucose tolerance curve was noted to fall to between 50 and 59 mg. per cent. Fifty-nine per cent of these patients had suggestive or positive symptoms of hypoglycemia, but only 29 per cent of them had an organic basis for the alteration in glucose metabolism. In 25 patients the low point in the glucose tolerance curve was between 60 and 70 mg. per cent. On analysis it was shown that 48 per cent of them had definite or suggestive symptoms, but only 28 per cent were suffering with organic conditions which might be the cause of the abnormal response.

These results offer us an interesting comparison between the cause and effect of low blood sugar concentrations during glucose tolerance tests and low unprovoked, fasting blood sugar levels. In the latter condition, the lowest sugar determinations were generally found associated with and dependent on definite pathologic processes. In the former the large majority of the lowest blood sugar levels were found associated with functional states.

It is unfortunate that so few glucose tolerance tests were made on the cases of parenchymatous liver disease that no conclusions can be drawn. In Addison's disease the glucose tolerance test varied with the condition of the patient. Before the institution of treatment or during the crises, a low blood sugar was found in the fasting stage and during the performance of the glucose tolerance test. After the institution of successful therapeusis there was an approach to or an attainment of a normal range. The patients with renal glycosuria showed all types of curve but rarely exhibited symptoms. The flat type of curve was found with greatest frequency in patients whose basal metabolic rate was well below normal.

There is a number of circumstances in which two or more glucose tolerance tests have been done on the same patient within a short period of time and the results of which have been divergent; so much so that typical diabetic responses have been found only a few days or a week from the time of subnormal elevations due to the ingestion of glucose. We cannot explain this finding.

SUMMARY AND CONCLUSION

1. We have given certain findings on 341 patients whose blood sugar, uninfluenced by insulin injection, was found at some time to be below 70 mg. per cent. Also on 63 patients whose blood sugar was in the 70's.

2. Hypoglycemia has been found associated with a large number of pathologic conditions. In these con-

ditions symptoms pathognomonic of hypoglycemia were found in 8.9 per cent of the cases. Suggestive symptoms were present in 20 per cent.

3. In patients with symptomatic functional hypoglycemia, symptoms may appear at a higher level of blood sugar than in patients with a recognizable basis for their hypoglycemia.

4. Except for the cases of symptomatic functional hyperglycemia and of epilepsy there are relatively few other instances where patients with definite symptoms of hypoglycemia had no recognizable basis for their hypoglycemia.

5. In the body of the article we have shown that a number of laboratory and clinical data could not be correlated with hypoglycemia. These are too numerous to renumerate.

6. We believe that there is a number of individuals with symptoms of hypoglycemia of unexplained etiology which we classify as "symptomatic functional hypoglycemia." We do not believe that at this time one is justified in diagnosing them as cases of hyperinsulinism.

7. It is our belief that many individuals become accustomed to or do not react to a lowered blood sugar, that would produce symptoms in others. This is true particularly of the cases of hypoglycemia arising from an organic basis.

8. We wish to express our belief that one should be very cautious in accepting a lowered blood sugar concentration as a cause of that vague symptom-complex which is especially typified by the psychoneurotic individual.

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The Relation of the Hydrogen Ion Concentration of Bile to the Formation of Gall Stones*

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IN spite of the numerous hypotheses concerning the formation of gall stones, no explanation has yet been advanced that adequately accounts for all of the phenomena involved. The evidence offered by Walsh and Ivy (1) in our opinion, more completely explains the immediate chemical factors concerned in maintaining the stone forming elements of bile in solution, than any theory suggested thus far.

Aschoff (2), Torinoumi (3), and others have noted the fact that cholesterol is the essential building material from which the framework of a gall stone is constructed. In the absence of cholesterol the other ingredients usually found in gall stones do not form more than a compact precipitate. Hence, the mechanisms by which cholesterol is held in solution are the *same mechanisms* which prevent gall stone formation.

Walsh and Ivy's evidence is based upon the previously established observation (4, 5, 6, 7), that human gall stones are readily dissolved in dog gall bladder bile both in the living animal and in vitro. An analysis of this phenomena in an effort to find the fraction of bile responsible, revealed that the greatest difference between human and dog bile was in the ratio of the non-saponifiable (cholesterol) to the saponifiable (fats and fatty acids) substances in the bile. On the basis of their experiments, the significant difference between human and dog bile did not revolve around the cholesterol content but around the relatively tremendous difference in content of fats and fatty acids. They concluded that the solubility of cholesterol in bile depends upon an interrelationship between: (1) fats and fatty acids; (2) bile salts or bile acids which act either by holding the fats and fatty acids in aqueous solution or by combining with fatty acids to form soaps.

More recently Feldman, Morrison and Krantz (8) have reported that the acidity of bile is a significant factor in explaining the reasons for the dissolution of human gall stones in the bile of certain animals. Their arguments are based upon their observations that human gall stones dissolve in the gall bladder of the dog which has an acid bile but do not dissolve in the gall bladder of the guinea pig which has an alkaline bile.

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In the course of our experiments on the factors concerned in gall stone formation we have obtained considerable data on the relationship between the hydrogen ion concentration of bile and the dissolution of gall stones. The object of this report is to present our findings concerning this phase of the studies.

METHODS

The relationship of the hydrogen ion concentration of the bile and the solution of gall stones was studied in two ways:

Method 1: Following in general the procedure used by Walsh and Ivy, human gall stones were weighed and placed in the gall bladders of dogs. After an interval of 65 days, the dogs were either re-operated or sacrificed and before the stones were removed, the bile was aspirated from the gall bladder for analysis. As a routine procedure, hydrogen ion concentration determinations were made on the bile so obtained. In some animals bile was aspirated at the time of operation so analyses on two samples from the same dog could be carried out.

Method 2: Another group of human gall stones, similar in character and obtained from the same human gall bladder, were weighed, wrapped in gauze to prevent mechanical injury and suspended in flasks to which was added either acid or alkaline bile. These flasks were then placed in a mechanical shaking device operating at a speed of 25-30 half revolutions per minute. The stones were shaken continuously for 7 days in a constant temperature chamber at 39° C.

TABLE I-A

Rate of dissolution of human gall stones in the gall bladder of the dog in 65 days. All stones from the same human gall bladder

Dog	Original Weight	Final Weight	Weight Loss	% Loss	pH
1	0.4893 gm.	0.0 gm.	0.4893 gm.	100.0	7.6
2	0.4372	0.0	0.4372	100.0	6.8
3	0.3186	0.0073	0.3113	98.0	6.7
4	0.4562	0.0268	0.4294	94.1	6.5
5	0.5235	0.0324	0.4821	93.7	7.5
6	0.7341	0.0613	0.6728	91.6	7.4
7	0.4671	0.0407	0.4264	91.2	6.8
8	0.3981	0.0489	0.3492	87.7	6.5
9	0.4934	0.0666	0.4268	86.5	7.2
10	0.5145	0.0774	0.4371	84.9	7.4
11	0.4651	0.0703	0.3949	84.9	6.8
12	0.4805	0.0754	0.4051	84.3	7.1
13	0.4189	0.0670	0.3519	84.0	7.0
14	0.5727	0.1030	0.4697	82.0	7.5
15	0.3404	0.0637	0.2767	81.3	6.9
16	0.6150	0.1407	0.4743	77.1	7.2
17	0.4351	0.1012	0.3339	76.7	7.2
18	0.5752	0.1502	0.4250	73.8	7.5
19	0.6150	0.1690	0.4460	72.5	6.4
20	0.4221	0.1280	0.2941	69.6	6.9
21	0.4002	0.1478	0.2524	63.0	7.5
22	0.4600	0.2035	0.2565	55.7	7.7
	MEAN			83.2	7.9
	PROBABLE ERROR ±			1.67	0.0175

The bile used in these experiments was pooled gall bladder bile from a number of cattle as received from a local packing firm. Part of this bile was buffered to a pH of 4.5-5.0 and part to a pH of 8.4-9.0. The bile in the flasks was replaced by fresh bile every 2 days. Similar experiments were carried out using bile obtained from dogs with chronic biliary fistulas and from human drainage operations.

In a third group of studies quantitative chemical analyses of the human, beef, and dog bile were performed using a specially modified analytical technique devised by one of us (K.K.J.). Mucin, non-saponifiable (cholesterol) and saponifiable (fats and fatty acids) fractions were determined. In addition to these analyses, pooled bile obtained from 18 normal guinea pigs was analyzed by similar methods for the purpose of comparison.

TABLE I-B

Determinations of pH of dog gall bladder bile at the time of operation for insertion of a stone and 65 days later at time of removal of stone. All stones from same human gall bladder as in Table I-A

Dog	Per Cent Dissolution	pH First Determination	pH After 65 Days
1	72.7	6.8	6.8
2	98.5	6.3	6.0
3	69.6	6.8	6.8
4	100.0	7.5	7.5
5	88.2	6.5	7.0
6	68.4	6.8	6.8
7	100.0	7.3	7.5
8	73.6	6.9	7.0
MEAN	85.2	6.85	6.92

RESULTS

Normally there is a wide variation in the rate with which dogs dissolve human gall stones when experimentally placed in their gall bladders. Unless stones obtained from the same human gall bladder are used in a large series of animals it is difficult to evaluate results upon a comparable basis due to the variability in the character of the stones. Table I-A shows the results of our findings in 22 normal dogs in which stones from the same human gall bladder were allowed to remain for 65 days. Table I-B shows the results of a similar group of dogs, eight in number, using stones from the same gall bladder as above, but in which determinations of pH of the bile were made both at the beginning and at the end of the 65 day period. It will be observed that there is no correlation of the variation in the rate of dissolution with the values obtained for the hydrogen ion concentration of the bile. The pH determinations, of course, reflect only one or two determinations and do not indicate the possible daily variations that may occur.

TABLES I-A AND I-B

Forty experiments were performed using acid and alkaline bile in vitro. Tables II and III respectively show the results of these studies. Comparing the mean values for the rates of dissolution in the acid and alkaline bile, it will be observed that the rate of dissolution in acid beef bile was 4.6 per cent greater than

in the alkaline. Statistical analysis of the results, however, shows there to be a combined probable error of ± 3.59 per cent in the two series. Therefore, there is no significant difference between the rates of dissolution in acid and alkaline beef bile.

TABLES II AND III

Twenty experiments were performed with acid and alkaline bile obtained from dogs with biliary fistulas. These results were tabulated in Tables IV and V and

TABLE II

Rate of dissolution of human gall stones when shaken constantly in Vitro in acid beef gall bladder bile buffered to pH 4.5-5.0 for 7 days

Stone	Original Weight	Final Weight	Weight Loss	% Loss
1	2.0106 gm.	1.9050 gm.	0.1056 gm.	5.2
2	1.4698	1.4300	0.0398	2.7
3	1.9050	1.6160	0.2890	15.1
4	1.4300	1.0470	0.3830	26.7
5	0.5270	0.4000	0.1270	24.1
6	0.7160	0.5880	0.1280	17.8
7	0.4850	0.3450	0.1400	28.9
8	0.7800	0.3600	0.4200	53.8
9	0.2800	0.2350	0.0450	16.0
10	0.3370	0.2670	0.0700	27.7
11	0.3970	0.6020	0.2050*	51.6*
12	0.3180	0.2460	0.0720	22.6
13	0.4820	0.3720	0.1100	22.8
14	0.3050	0.2480	0.0570	18.6
15	0.2720	0.2130	0.0590	21.6
16	0.3340	0.2700	0.0640	19.1
17	0.5020	0.4560	0.0460	9.1
18	0.4180	0.3710	0.0470	11.2
19	0.4000	0.3630	0.0470	11.7
20	0.4450	0.3950	0.0500	11.2
		MEAN		15.7
		PROBABLE ERROR ±		2.87

*Gain

show there to be a difference of 1.0 per cent in the rates of dissolution in the acid and alkaline bile. Statistical analysis of the results, however, demonstrate that the difference is definitely not significant when the probable error is computed.

TABLES IV AND V

Tables VI and VII show the rates of dissolution in the acid and alkaline human fistula bile. As with the series of experiments using the beef and dog bile, no statistically significant difference was obtained. In these experiments a difference of 2.88 per cent was found in the means of the rates of dissolution of the two series. This difference, however, is subject to a probable error of ± 1.44 per cent.

TABLES VI AND VII

Quantitative analyses of the bile obtained from humans, dogs, guinea pigs, and the ox offer a much more comprehensive explanation of the differences in the rates of dissolution of human gall stones when experimentally placed in various animals. Table VIII shows the results of these analyses.

TABLE VIII

It will be seen that the human bile closely approximates that of the ox and guinea pig as far as the fatty acid—cholesterol fraction is concerned. Both man and ox are spontaneous formers of gall stones and the

TABLE III

Rate of dissolution of human gall stones when shaken constantly in Vitro in alkaline beef gall bladder bile buffered to pH 8.4-9.0 for 7 days

Stone	Original Weight	Final Weight	Weight Loss	% Loss
1	1.7206 gm.	1.5750 gm.	0.1456 gm.	8.5
2	1.6200	1.5830	0.0370	2.3
3	1.5750	1.4290	0.1460	9.3
4	1.5830	1.2930	0.2900	18.3
5	0.5350	0.4850	0.0500	9.3
6	0.8420	0.7800	0.0620	7.3
7	0.4000	0.3180	0.0820	20.5
8	0.5880	0.4820	0.1060	18.0
9	0.3350	0.3050	0.0300	8.9
10	0.2920	0.2720	0.0200	6.8
11	0.3650	0.3340	0.0310	8.7
12	0.5120	0.4660	0.0460	8.9
13	0.3600	0.3130	0.0470	13.0
14	0.2350	0.1960	0.0390	16.5
15	0.2670	0.2210	0.0460	17.2
16	0.6020	0.5100	0.0920	15.2
17	0.3830	0.3500	0.0330	8.6
18	0.4230	0.4000	0.0230	5.4
19	0.4000	0.3700	0.0300	7.5
20	0.1700	0.1460	0.0240	14.1
		MEAN		11.1
		PROBABLE ERROR ±		0.72

guinea pig does not dissolve human stones if placed in their gall bladders. Dogs on the other hand have a comparatively high concentration of fatty acids both in proportion to the other animals and in proportion to the amount of non-saponifiable material present in the bile. The ratios for the fatty acid fraction to the non-saponifiable material are as follows: Human drainage bile 1.4:1, Ox bile 6.75:1, Guinea pig bile 15:1, Dog gall bladder bile 20.3:1, and Dog fistula bile 18.1:1.

In comparing the fatty acid — non-saponifiable ratios, it will be observed that guinea pig gall bladder, bile almost approaches that of the dog as far as the relative concentration of these two components are concerned. It would appear, therefore, that human gall stones should dissolve in guinea pig gall bladder bile. Sufficient guinea pig bile, however, cannot be economically obtained in the quantities required for testing. A careful study of the data presented by Feldman, Morrison, and Krantz, in which they report no dissolution of human gall stones in the gall bladder

of the guinea pig, shows that small weight losses actually did occur. When their data is re-computed upon a percentage basis, weight losses of 2.2, 2.2, 15.8, 17.6 per cent respectively occurred in four of their seven experiments, running the animals from 110 to

TABLE IV

Rate of dissolution of human gall stones when shaken constantly in Vitro in acid dog hepatic bile buffered to pH 4.5-5.0 for 7 days

Stone	Original Weight	Final Weight	Weight Loss	% Loss
1	0.4380 gm.	0.4110 gm.	0.0270 gm.	6.4
2	0.4760	0.4380	0.0380	7.9
3	0.2480	0.2130	0.0350	14.1
4	0.2130	0.1830	0.0300	14.0
5	0.2700	0.2370	0.0330	12.2
6	0.4400	0.4180	0.0220	5.0
7	0.2820	0.2670	0.0150	5.3
8	0.5280	0.5020	0.0260	4.4
9	0.4660	0.4450	0.0210	4.5
10	0.4010	0.3830	0.0180	4.4
		MEAN		7.8
		PROBABLE ERROR ±		0.88

121 days. In two instances no change in weight occurred and in one, a gain of 6.0 per cent took place. Due to the small size of the guinea pig gall bladder, a further factor must be considered, namely, the insertion of a human gall stone even though it may be

TABLE V

Rate of dissolution of human gall stones when shaken constantly in Vitro in alkaline dog hepatic bile buffered to pH 8.4-9.0 for 7 days

Stone	Original Weight	Final Weight	Weight Loss	% Loss
1	0.4660 gm.	0.4400 gm.	0.0260 gm.	5.5
2	0.3130	0.2820	0.0310	9.9
3	0.5570	0.5280	0.0290	5.2
4	0.4930	0.4660	0.0270	5.4
5	0.4250	0.4010	0.0240	5.6
6	0.4110	0.4000	0.0110	2.6
7	0.4380	0.4230	0.0150	3.4
8	0.2130	0.1830	0.0300	14.0
9	0.1830	0.1700	0.0130	7.1
10	0.2370	0.2180	0.0190	8.0
		MEAN		6.8
		PROBABLE ERROR ±		0.7

small in size, into a viscus the size of the guinea pig's, of necessity brings about a marked impairment of filling and activity. Some idea of the size of the guinea pig gall bladder may be obtained when only 5.0 c.c. of bile were obtained from 18 normal guinea pig gall bladders for our analyses.

DISCUSSION

It is becoming more and more apparent that gall stones occur as the result of a disturbed chemistry of the bile. Whether this disturbance is the direct result of pathologic changes in the liver, aberrations in metabolism, or stasis and infection involving the gall bladder is still uncertain. Certainly the immediate

TABLE VI

Rate of dissolution of human gall stones when shaken constantly in Vitro in acid human fistula bile buffered to pH 4.5-5.0 for 7 days

Stone	Original Weight	Final Weight	Weight Loss	% Loss
1	0.4560 gm.	0.4400 gm.	0.0160 gm.	3.5
2	0.3710	0.3470	0.0240	6.4
3	0.3630	0.3460	0.0170	4.6
4	0.3950	0.3740	0.0210	5.3
5	0.3500	0.3490	0.0010	0.3
		MEAN		4.02
		PROBABLE ERROR ±		0.69

factor in stone formation is a change in the relative concentration of the various biliary constituents.

Andrews, Schoenheimer, and Hrdina (9) have suggested that gall stones form as the result of an abnormal diffusion of bile salts out of the gall bladder, allowing the cholesterol, which is held in solution by the bile salts to precipitate out and form stones. It was shown that while the normal dog's gall bladder absorbed neither cholesterol nor bile salts in appreciable amounts, the abnormal gall bladder absorbed bile salts and thus lowered the ability of the bile to hold cholesterol in solution. Subsequent observations by these workers on patients with cholelethiasis subjected to surgery confirmed this hypothesis. On the basis of Walsh and Ivy's observations, however, we believe this mechanism to be secondary to changes

TABLE VII

Rate of dissolution of human gall stones when shaken constantly in Vitro in alkaline human fistula bile buffered to pH 8.4-9.0 for 7 days

Stone	Original Weight	Final Weight	Weight Loss	% Loss
1	0.4000 gm.	0.3980 gm.	0.0020 gm.	0.5
2	0.3700	0.3690	0.0010	0.2
3	0.1460	0.1390	0.0070	4.7
4	0.2400	0.2400	0.0	0.0
5	0.3270	0.3260	0.0010	0.3
		MEAN		1.14
		PROBABLE ERROR ±		0.75

occurring in the fatty acid component since, in the absence of bile salts, fatty acids are precipitated as soon as the bile becomes acid in reaction. Their studies demonstrate that bile salts are secondary in the process of keeping cholesterol in solution and act by virtue of their combination with the fatty acids of the bile. Using various fatty acids as solvents, they reported that stones increased in weight in butyric acid

but lost markedly in oleic, lauric, or myristic acid solutions of a 1 per cent concentration in a pH 8 buffer solution. Greatest dissolution was obtained in lauric acid. It was found that better solvent action could be obtained at a more alkaline reaction. Walsh and Ivy explained this upon the basis that there was more soap available to hold the fatty acid in solution. It was further demonstrated that fatty acid was apparently the most active principle since in vitro, pure fatty acids dissolve gall stones readily whereas neutral fats or bile salts do not have such marked solvent action. The addition of bile salts, however, to a lauric acid solution increases the solvent capacity of the solution.

TABLE VIII

Results of quantitative analyses of human, dog, ox, and Guinea Pig bile

Animal	Bile Fractions—Figures in Grams /100 c.c. Bile			Remarks	Ratio—Fa: Non-S
	Alcoholic Precipitate (Mucin)	Non-Saponifiable	Fatty Acids		
MAN (Drainage Bile)	0.207	0.149	0.211	Results of analysis — 27 samples on 3 patients	1.4:1
OX (Gall Bladder Bile)	0.350	0.810	0.540	4 analyses from 2 pooled stockyard samples	6.75:1
GUINEA PIG Gall Bladder Bile)	0.500	0.020	0.303	Pooled samples from 18 guinea pigs	15:1
DOG (Gall Bladder Bile)	1.521	0.142	2.850	Mean value from 8 normal dogs	20.3:1
DOG (Hepatic Bile)	0.316	0.018	0.328	Mean value from 3 dogs with chronic biliary fistulas	18.1:1

On the basis of our studies it does not appear that the hydrogen ion concentration of the bile has any prime significance in the mechanism whereby cholesterol is held in solution. In the in vitro experiments, the trend, if any, was for somewhat greater solution at an acid pH but the difference between the rates of solution in the acid and alkaline bile cannot be considered significant in view of the statistical analyses.

The quantitative analyses of human, dog, guinea pig, and ox bile demonstrate quite definitely that there are variations in the relative proportions of fatty acids to the non-saponifiable material of the bile which must be considered significant. A comparison of these figures offers a much more plausible explanation for the differences in stone solvent properties of the bile of various animals than that revealed by a study of hydrogen ion concentration.

CONCLUSIONS

1. No statistically significant difference was obtained in the relative solvent action of acid and alkaline bile from the ox, dog, and man on human gall stones of the mixed cholesterol variety.

2. Comparison of quantitative chemical analyses of human, dog, ox, and guinea pig bile shows that there are distinct differences in the relative concentration of the fatty acid to the non-saponifiable (cholesterol) fraction of the bile. We believe these variations to account for the difference in the solvent action of the bile of various animals rather than being due to variations in hydrogen ion concentration.

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Is Uremia an Allergic Manifestation?

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MEDICAL science, the same as the physical sciences, has arrived at a stage when much of its hitherto accepted knowledge must be reevaluated and rewritten. Due to the large number of investigators in medicine and the ancillary sciences, medical knowledge has increased very rapidly in recent years. This has created an unusual problem, in that the lag in its application bids well to defeat the benefits from these new discoveries. Attention must be given to methods that will disseminate our new knowledge. Since the work of the Argentinian physiologist Houssay, the older conception that the pancreas regulates the glucose content of the blood must be modified to a great extent. In the same way the older belief that an elevation in the urea nitrogen of the blood depends on a structural lesion in the kidney is no longer tenable. There are many conditions that may produce uremia

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in the presence of normal kidneys. It is the purpose of this paper to review some recent developments on the subject of uremia and to show that in many cases the uremia is best explained on a sensitivity or allergic basis.

The usual teaching associates uremia with a kidney lesion of sufficient magnitude to cause renal impairment. Such conditions as diffuse glomerulonephritis and vascular nephritis can produce sufficient renal impairment to cause uremia. Such are the "true uremias." Another important syndrome is "pseudouremia." Olivet (1) claims that in pseudouremia the kidney function is good and the urea N. is not much elevated. In his 6 cases the urea in the blood did not exceed 50 mg. per cent. He quotes Volhard who states that the important symptoms in pseudouremia are headache, disturbances of the senses chiefly the eye and ear, aphasia, acute psychic disturbances with mental aberrations that pass over quickly. This is very much similar to what is seen in hypertensive encephalopathy.

The uremia chosen for discussion in this paper centers around the gastro-intestinal tract and is termed by various writers, enterorenal syndrome (2), uremia syndrome (3), manque de sel, hepatorenal disease (4), gastric uremia (5), and extrarenal uremia (5, 6). The clinical picture is as follows: It is usually an acute process appearing rather abruptly and running a rapid downhill course. The syndrome begins with malaise, headache, muscular weakness, sleepiness and vomiting. This is followed by hiccup, restlessness, dry tongue, intestinal paresis, stupor and coma. In some, renal function is good; in others there is anuria. Cerebral symptoms and icterus may be present. A shock syndrome is usually associated as evidenced by tachycardia, dyspnea, cyanosis, fall in blood pressure, and subnormal temperature. Azotemia is usually present, being due, in most instances, to an increase in urea; but an increase in creatinine has been observed (7, 8). There is usually no early history of nephritis and the kidneys are normal on autopsy. However, a few investigators have reported kidney lesions in such cases but the reports are not uniform and on the whole poorly described and unconvincing. Cooper (7) and also McCance (8) who have devoted much time to this subject are both of the opinion that the uremia is functional and that renal excretion remains normal or is only slightly impaired.

Uremia or high blood urea has been reported in the following conditions: Gastro-intestinal intoxication (5), acidosis (9, 10, 11), alkalosis (12, 13), salt deficiency (14, 12), pancreatic insufficiency (15), hypohydration (6, 9), post-operatively (16), diabetic coma (17), hypertension (3), prostatic disease (18), after blood transfusion (19), with adrenal insufficiency (20, 21), with sterile abscess (22, 23), pleuritis (22, 23), anaphylaxis (24), pneumonia (22), coronary thrombosis (23), and with liver injury (23). Uremia has also been reported when magnesium or calcium is taken into the body over long periods (26, 27), and with disturbances of calcium metabolism as in hyperparathyroidism (28) and in myeloma. In such cases, as well as in prostatic disease, obstruction by mechanical means, by calculi, and nephrocalcinosis, may play a factor in the uremia but further work along this line is required. In most of the other conditions the uremia is probably extrarenal. Some of these will now be considered in greater detail.

GASTRO-INTESTINAL INTOXICATION

Under this grouping could be included the uremia with high intestinal obstruction, also uremia after intestinal allergy, food poisoning, ulcer, colitis, gastro-intestinal bleeding and the uremia with paralytic ileus.

High Intestinal Obstruction: That high intestinal obstruction is associated with an elevation of the N. P. N. which is made up for the most part of urea has been known for a long time. There are several other equally important principles that could also be mentioned:

1. If the intestinal contents above an obstruction is injected intravenously into another animal, "toxin injection," that animal will show almost the same clinical picture as the animal with the obstruction.
2. The symptoms in high intestinal obstruction are usually explained by two factors:
   A. Salt deficiency and hypohydration.
   B. Toxemia or shock.

If the symptoms come on quickly and death occurs in a few days, the latter factor is the more important. In recent years the toxic idea has been losing ground and the idea that death is due to shock and fluid loss has been gaining adherents. The idea, however, is not new and was expressed by Braun and Boruttau (29) as early as 1908.

3. If the bowel of an animal is obstructed by the use of clamps so there is no strangulation and the circulation is not cut off, the animal will survive a long time if water is supplied, dying finally from starvation. In this way the element of shock is eliminated.

The above ideas were taken from Cooper's review of the subject in 1928, he gives the symptoms in obstruction as follows:

1. Vomiting
2. Dehydration
3. Tremors and weakness of the hind legs
4. Weak and rapid pulse
5. Drop in the blood pressure
6. Coma and death.

The clinical pathology is as follows:

Blood:
1. Leucopenia
2. High non-protein nitrogen
3. High Co_2 combining power
4. Low chloride content.

Urine:
1. Scanty
2. Slight trace of albumin
3. The N. P. N. excretion is much increased
4. Low chloride excretion.

The clinical picture in obstruction is stressed because it resembles very closely the picture of extrarenal uremia and is also seen in several other conditions that appear to be related. More will be said about this later.

Foster and Hausler (30) tied off loops of bowel in animals and found an increase in the urea of the blood. They believed this was due to retention since all the animals dying from strangulation had anuria. Most investigators, however, believe that the uremia is due to excessive protein destruction and in spite of

good kidney function, the urea cannot be excreted quickly enough. What the true modus operandi is we cannot say at the present time. It appears that both factors, retention and urea overproduction may be operative.

Uremia with Gastro-Intestinal Lesions: The following case shows the development of extrarenal uremia in a patient with ulcer; the picture of shock is evident.

Case 1. A male 49 years of age was admitted to the Cook County Hospital with convulsions and coma. Two days ago he felt poorly and he had several attacks of convulsions. For 15 years he had had frequent attacks of stomach trouble with vomiting. The pulse was 96, respirations 34, temperature 100 and blood pressure 126 mm. of hg. systolic and 78 diastolic. The pupils were equal and reacted. The spinal fluid was clear and not under pressure. The urine showed 4 plus albumin, the phenol test was faintly positive and the urea N. 100 mg. per cent. There were convulsive movements of the extremities. The blood pressure fell to 70 over 60 and he died the next day in what was considered a uremic state. Autopsy was performed by Dr. R. H. Jaffe. The stomach was tremendously dilated and in the duodenum there was a constricting scar also an ulcer. The kidney changes were minimal.

Mallory (31) reported a case in a young girl of 22 with a history of hypertension. Her symptoms came on 10 minutes after eating a meal. She was operated and a gangrenous appendix removed; thirteen days later she died in uremia. Kiefer (32) reported a case where a high N. P. N. was observed in a patient with diarrhea. One month later an X-ray showed the characteristic picture of ulcerative colitis.

Gastro-Intestinal Bleeding: Sucic (33) cited several cases with an elevated urea N. following gastro-intestinal bleeding. He also showed that bleeding from other parts of the body such as hemoptysis and venesection are not followed by uremia. He also showed that this was not due to blood digestion and since none of his cases showed nephritis, renal insufficiency could not be accepted as a cause for the elevated urea. Two of his cases follow:

Case 2. The patient had a duodenal ulcer, the urea N. was 64 mg. per cent. Ten days later there was melena and the urea rose to 92 mg. per cent and the blood chloride was 426.

Case 3. This patient had ulcers in the stomach and duodenum. There was hematemesis and the urea was found to be 120 mg. per cent. After transfusion it dropped to 84, the patient recovered.

Christiansen (34) does not believe that patients with bleeding peptic ulcer actually die from loss of blood; he suggests uremia as the cause of death in such patients.

Meyler (6) has reported similar cases. He advances the idea that all extrarenal uremias are in reality "production uremias" due to the great destruction of protein and the kidneys cannot excrete the excess nitrogen. It is well to mention at this time, that gastro-intestinal bleeding occurs for the most part with ulcer and colitis. We do not know the cause for these conditions at the present time but it is of interest that the literature contains many references to their allergic nature. Kern (35), Gay (36), Clarke (37) and Ryss, et al (38) claim that peptic ulcer is allergic in nature; whereas Rowe (39), Duke (40), Vaughn (41), Bisset (42), Hollander (43), Beecher (44) and Strumpel (45) claim the same for colitis. Later, evidence will be presented to show that "extrarenal uremia" occurring in such patients is probably best explained as a "hypersensitivity" or "allergy." It might be further added that the intestinal bleeding and uremia seen by Sucic and Meyler are also seen in anaphylactic shock.

ACIDOSIS, ALKALOSIS AND HYPOHYDRATION

The association of uremia and acidosis is discussed by Andrews (10, 11), also Fantus (9). Andrews explains the anuria in such cases by the tendency on the part of the tissues to fix water in acid medium resulting in hypohydration. He produced a uremia in animals in the presence of normal kidneys. Salt infusions aggravated the condition. It is possible that acidosis is the dominant factor in the uremia seen with diabetic coma, it may also be a factor in pancreatitis or pancreatic insufficiency.

Uremia can also occur with alkalosis. Hurst (13) states: "I have seen some patients who were thought to be dying from uremia, but who were really suffering from alkalosis and who were saved by discontinuing alkalies." The following cases taken from Cooke (12) are instructive:

Case 4. A male 46 years of age was put on a diet and alkalies for 12 days. He developed malaise and pains all over his body. The urine showed albumin and casts. The urea N. was 173 mg. per cent. The alkalies were stopped and after eight days, the urea N. had dropped to 28 mg.

Case 5. Another patient had taken sodium bicarbonate for 8 years. One day he developed intense vomiting, irritability, headache, and tetany. The plasma carbonate was 97, the N. P. N. 90 and urea N. 71 mg. per cent. On ammonium chloride therapy, these same values dropped to 67, 43, and 17 respectively.

Comment: In the first case, it appears as though there was a hypersensitivity to the alkali powder. In the second case, the evidence is not nearly so clear, and we could ask why a man should suddenly become sick from a powder that he had been taking with comfort for 8 years? In reading over the cases cited in the literature as due to alkalosis many are found to be similar to the last case and some authors admit that some factor exclusive of alkalosis must play a part. Cooke states: "A patient who has once had an attack of uncompensated alkalosis always shows himself intolerant to alkalies in the future." He also stresses the resemblance between the blood picture in alkalosis and excessive vomiting. The latter symptom is an early one in anaphylactic shock and it seems that much of the evidence points to the uremia in alkalosis as a manifestation of sensitivity to alkalies.

Hypohydration as a cause of uremia is widely accepted. A uremia has even been produced in animals by rapid diuresis. In hypohydration the uremia is explained by some writers (6) as resulting from excessive protein destruction, being further aggravated by anuria which is frequently seen in such cases. The fact that certain forms of uremia may be corrected by the administration of water only, speaks for the importance of water in nitrogen metabolism or in its elimination.

SALT DEFICIENCY OR "MANQUE DE SEL"

The uremia due to salt deficiency and the growing importance of sodium in disease generally, has been extensively discussed by Blum (46), Koranyi, Graber, Haden and Orr (14), Mellinghoff (47), Keller (48),

McCance (8), Harrop (20), Siedeck and ZukerKandl (49) and others. A review of this important subject cannot be undertaken at the present time but reference may be made to some of the above publications. The importance of sodium chloride in uremia and in nitrogen metabolism is very incompletely understood at the present time. In the first place, it is very difficult to obtain a pure sodium chloride deficiency because in most instances it is complicated by water loss, alkalosis, and usually some other illness. To produce a hypochloremia in normal persons is a difficult thing as was shown by the work of McCance. Every one interested in this subject should read his Goulstonian lectures (6). McCance made human subjects salt deficient by the use of a salt free diet and the use of a daily sweating chamber. This produced anorexia, thirst, cramps, and anginal like pains on exertion, but all subjects were able to continue their occupations. They also showed hemoconcentration, a rise in the urea N., a drop in the plasma chloride and plasma sodium and a negative nitrogen balance. One subject failed to show a rise in the urea N., it was also very difficult to make her salt deficient. We must accept from this work that salt deficiency uncomplicated by water loss is associated with a rise in the urea N. However, under clinical conditions an uncomplicated hypochloremia is probably a rarity. Certainly a parallel between the hypochloremia and the elevation in the urea N. cannot be established in such cases. Kerpel-Fronius and Butler (50) could find very little parallism between these. They also observed that the nitrogen retention could be removed by water without salt. Kline (51) reports a case of Addison's disease where salt deprivation caused the plasma sodium to drop to 223 mg. per cent but the rise in N. P. N. was only 12.8 mg. per cent. In another case evidently not Addison's disease after 7 days of strict salt deprivation there was very little if any change in either the plasma sodium or N. P. N. Contrast with Blum's case (v.i.). However many investigators hold that the uremia is due to salt deficiency. Cooper quotes Haden and Orr who using dogs with simple high obstruction prolonged life with salt solution and as long as they kept the blood chlorides at normal level the other blood changes did not occur. It is well to remember, however, that dogs with an obstruction which is produced by clamps so that no injury to the circulation occurs, may not develop the syndrome at all but will live for weeks, dying in the end from starvation, as long as the water balance is maintained. It might also be said that the drop in the azotemia seen in some cases after salt infusions may be due to the correction of the anuria by overcoming renal spasm as was shown by Takeda (53).

One reason why confusion exists regarding the importance of reduced chlorides in uremia, is that uremia may exist with different conditions that vary as to their pathogenesis. This is well borne out in the case of high intestinal obstruction where there are at least 2 factors involved, and either one may of itself be a cause of uremia, these are:

1. Toxemia or shock.
2. Dehydration and salt deficiency.

If death occurs early it is usually due to shock, if the patient survives for a longer time the factor of dehydration and salt loss may enter because of persistent vomiting. Foster and Hausler (54), also Gatch, Trusler and Ayers (55) showed that water and salt were of no benefit in the treatment of strangulation where toxemia (shock) has the upper hand. However, in dehydration it may be of distinct value.

PANCREATIC INSUFFICIENCY

The loss of pancreatic juices may produce uremia as was shown by Walters and Bollman (56) and confirmed by Bolton (57). By experiments on dogs, they showed that continued loss of pancreatic juice through a duodenal fistula resulted in uremia and death in 7 days. There was no change in the blood chlorides or the Co_2 combining power. Life was not saved by salt.

How pancreatic insufficiency is related to uremia is not known. However, Oelgoetz et al (58) claim that pancreatic insufficiency may cause allergy to foods. They state that normally sufficient pancreatic juice is secreted to combine with all the food eaten and so acts as a buffer. Food hypersensitivity is caused by "free food" free of pancreatic enzymes. Another explanation for this type of uremia is the one suggested by McCance. He points out that pancreatic juice is very rich in bicarbonate and its continued loss may result in acidosis.

BLOOD TRANSFUSION

The uremia following blood transfusion has been observed by several investigators. Bordley (19) reported 3 cases and collected 14 from the literature. De Gowin and Baldridge (59) reported 2 cases and point out the dangers of hemolysis even though the blood be compatible from the standpoint of agglutination. Both patients developed anuria followed by an elevated blood urea and death. The blood chlorides were normal in both instances 555 and 600 mg. and the authors also ruled out acidosis as the cause. They quote Mason and Mann who have shown that the intravenous injection of hemoglobin has a specific vasoconstriction effect on the kidney which can be relieved by the transfusion of compatible blood. The latter point was also shown by Hesse and Filatov (60) and is very important in therapy. However, Sellards and Minot have shown that hemoglobin itself may not produce anatomic or functional changes in the kidneys. In Bordley's cases the transfusion was followed by a febrile reaction with hemoglobinuria and oliguria. This was followed by an interval of symptomatic improvement, after which there was agitation, drowsiness and uremia. The appearance of the symptoms in 2 phases an early and a late, should be noted. This will be referred to later.

Several writers claim that the anuria in hemolytic shock is due to the blocking of the renal tubules with hemoglobin crystals. Such a belief is unlikely since it has been shown that hemoglobin itself may be harmless to the kidneys (v. s.). The clinical picture is also against such an interpretation because oliguria comes on suddenly, and with recovery there is a sudden diuresis. Wesselkin also Iljin claim that hemolytic shock resembles histamine shock and have demonstrated by kidney measurements that renal spasm is part of the acute phase of such shock (v.i.). Hypochloremia can be ruled out as the cause because in several cases the chloride values were normal (v.s.) and in uremia with hypochloremia there is usually diuresis. De Gowin and Baldridge claim to have ruled out acidosis also. There remains nothing but sensitivity to explain this uremia and the whole clinical

picture fits it quite well. The weakness, choking, dyspnea, continuous vomiting and coma is the picture of anaphylactic shock.

POST OPERATIVE UREMIA

The uremia that occurs post operatively has been investigated by the French physicians. Some of their ideas may be summed up as follows: Patients lose weight and feel weak after an operation, this should leave after 24 hours, if it persists there is danger of paralytic ileus. They think that this is in some way associated with nitrogen and salt metabolism and their reasoning is as follows:

1. After every operation there is an increase of urea in the blood and an increase of nitrogen in the urine which is due to the destruction of protein. At the same time there is a reduction in chlorides and in the red cell count.
2. There is a decrease of salt elimination in the urine.
3. Not only does the urea in the plasma increase but also the "azote residual" (the total non urea fraction of the N. P. N.?).
4. Sodium chloride has a neutralizing action for the toxic protein products of the wound. In the treatment of several post operative cases the N. P. N. was reduced by the use of 500 c.c. of 4 per cent sodium chloride.

The following case is one of post operative uremia reported by Gabriel and Lloyd Davies (61):

Case 6. A 55 year old male was diagnosed cancer of the rectum. The heart showed no abnormality, the blood pressure was 175 mm. of Hg. systolic and 125 diastolic. The blood urea was 67 mg. per cent. Colostomy was done under spinal anesthesia. 80 hours post operatively he began to vomit, there was dull abdominal pain, pulse 106, this was followed by hiccup. The abdomen was silent and there was distension. Continuous I. V. normal saline in 5 per cent glucose was given 10 ounces per hour, for 7 hours. Twenty-two hours after onset the pulse was 130 and the blood pressure 160 mm. Hg. systolic and 120 diastolic. The pulse gradually increased and the patient died in 48 hours. The urinary chlorides were absent despite the infusions of chlorides. The blood urea rose steadily suggesting a uremia, however, the Van Slyke clearance tests showed that the kidney function was unimpaired and urine with a very high urea concentration continued to be excreted.

Autopsy findings: The stomach and small bowel were distended to within 2 feet of the ileocecal valve. At this point the distention gradually faded and the small gut distal to this point and the colon were collapsed. No peritonitis and no adhesions were present in any part of the abdomen. There was no abnormality in any of the other organs.

Comment: In this case the uremia supervened with the kidneys functioning well. Salt infusions were without effect. The vomiting, hiccup and paralytic ileus are suggestive of the extrarenal uremia syndrome. Distension of the small bowel leaving the colon unaffected is characteristic of paralytic ileus. The rapid pulse is suggestive of shock. Large amounts of urea were being produced or urea was being reabsorbed. In this case, we are probably dealing with a true "production uremia."

UREMIA WITH DIABETIC COMA

Lyall and Anderson (62) cite 19 cases of diabetic coma with elevated urea N. They estimate that as high as 50 per cent of patients with diabetic coma also have an elevated urea N. Acidosis as a contributing factor must be considered. They cite this instance:

Case 7. In this patient with diabetic coma, there was a period of anuria lasting 4 days, during which time the urea rose to 230 mg. per cent. The plasma chloride was 580 mg. per cent.

McCance believes that this uremia does not depend on an organic change in the kidney. He states: "One must conclude that the abnormality is a temporary one of function only and not a permanent one of structure." Again in discussing salt deficiency, he says: "If the patient recovers from the intestinal obstruction or diabetic coma renal sequelae are never observed."

McCance believes that the blood picture in diabetes and in diabetic coma is in keeping with a salt deficiency. He quotes Haldane and Denny et al, who demonstrated that in severe experimental acidosis there is at first a large loss of fixed base, mostly sodium. There is also an increase in plasma proteins and hemoconcentration in comatose patients. He admits, however, that the latter can be caused by hypohydration, and it is well known that this also occurs in shock.

Lyall and Anderson quote Blum in the following case which shows a relation to salt deprivation:

Case 8. The blood sugar was 355, the alkali reserve 16 and the urea 55 mg. per cent. The patient improved and the urea fell to 45 mg. while the urine contained albumin and casts. Upon a chlorine free diet the urea rose to 480 mg. in six days while diuresis was good and the urine contained only a trace of albumin and casts. Upon giving salt by mouth the blood urea returned to normal.

Comment: Again we have a case of uremia with good diuresis which appears to be another instance of "production uremia." The relation of the azotemia to salt deprivation is most striking. This case should be compared with the work of McCance (v.s.) it is obvious that some persons are much more sensitive to salt deprivation than others.

The symptoms produced on the withdrawal of certain substances that the body has become accustomed to resemble very closely an anaphylactoid reaction. Ormislensky (63) claims that the withdrawal symptoms in opium addicts are similar to anaphylaxis and considers the reaction an allergic one. This raises a very interesting point but at the present time we can do little more than speculate about it.

Steinberg reported 2 cases of azotemia following coronary occlusion with a rise in the N. P. N. and death. At autopsy the kidneys were found to be normal in both cases. Mazer reported 3 cases of azotemia with tuberculosis of the adrenals; at autopsy, the kidneys were normal.

The uremia seen with adrenalectomy is probably a functional one, since renal function may often be restored by the use of cortin. There is evidence that the renal insufficiency is secondary to hypochloremia. The adrenal cortex contains a hormone which controls the kidney threshold for sodium and in its absence a sodium deficiency is manifest (64, 65). The use of sodium chloride in the treatment of experimental and clinical adrenal disease has been reported as successful in some cases (66) and unsuccessful in others. It is also worthy of note regarding the adrenals, that Dale was able to show that adrenalectomy enhanced

the toxic action of histamine and that the use of eucortone was found of therapeutic value in the "shock syndrome" following burns (68) (v.i.). Sweet (69) also Ellis found that dogs after suprarenalectomy died with symptoms very much similar to "toxin injection" and were able to recover a similar toxin from the intestinal tracts of such animals. Stewart and Rogoff described the following syndrome in adrenalectomized dogs:

1. Vomiting
2. Staggering
3. Tremor
4. Collapse
5. Weak pulse
6. Low blood pressure.

The blood showed:

1. Leucopenia
2. High N. P. N.
3. Rise in creatinine
4. Fall in chlorides.

The organs showed at autopsy:

1. Congestion of the Lungs
2. Congestion and hemorrhage in the G. I. tract.

Later it will be shown that the symptoms of food poisoning also resemble this syndrome very closely. Wilmer and Miller (70) were impressed by the similarity between adrenal insufficiency and allergic manifestations and injected adrenal cortical hormone in certain select cases of allergy. Some of these patients jority, there was a definite improvement in general health. Wyman (71) compared adrenal insufficiency to anaphylactic shock and histamine poisoning. Swingle (72) compared it to traumatic shock. Harrop (20) injected intraperitoneal glucose into intact dogs thereby causing a reduced plasma sodium and was able to produce the clinical picture of adrenalectomy.

THE RELATION OF EXTRARENAL UREMIA TO HISTAMINE SHOCK AND SEVERE BURNS

It must by now be apparent to the reader that a shock syndrome is a frequent accompaniment of extrarenal uremia and it is the shock and not the elevated urea that accounts for the severe collapse and the fatal outcome. An increased amount of urea in the blood is not incompatible with life. In the elasmobranch fishes it may reach one per cent. On the other hand the uremia syndrome may exist with a normal blood urea; Beaumont and Dodds, quoted by Andrews, have reported 4 such cases. The shock is probably the result of histamine release. Death in such cases may be due to fluid loss as the result of capillary atony as was shown by Braun and Boruttau (29) also Blalock (23). The collapse, fall in blood pressure and hemoconcentration speak for loss of extracellular fluids.

Clinically the picture of extrarenal uremia shows a close resemblance to, and may occur with the following conditions. In all of these conditions the shock syndrome is present and many workers have stressed the similarity to histamine poisoning (v.i.).

1. Severe burns
2. Food poisoning
3. Allergic manifestations
4. Anaphylaxis
5. Acute pancreatitis
6. Bilateral suprarenalectomy
7. Obstruction with strangulation of the bowel or mesentery
8. Hemolytic shock, etc.

Eppinger et al (74) described a syndrome after the ingestion of spoiled meat with the following symptoms:

1. Vomiting
2. Collapse
3. Cold sweats
4. Signs of peritonitis
5. Hemoconcentration
6. Leucopenia
7. Albuminuria and cylinduria.

The pathologic picture of the internal organs was as follows:

1. The stomach mucosa was dark and covered with erosions and ulcerations
2. The duodenum was similar and the picture was intense in the colon
3. The liver showed the picture of "tissue albuminuria."

They noted a relation between food poisoning and histamine poisoning. They isolated an "allylamine" product from spoiled meat and were able to produce a similar picture in dogs by injecting this substance. Moon (75) claims that the pathologic picture in severe burns is almost identical to those found in shock. He claims that histamine is released by the burning of the skin and may be responsible for the shock.

The similarity between anaphylactic shock and histamine shock has been stressed by Dale and Laidlow (76), Abel and Kubata (77) and Dragstedt and Mead (78). Loeper et al (79) and also Unger et al (80) were able to produce gastro-intestinal hemorrhage with histamine. Similarly Gregoire (81) observed hemorrhagic pancreatitis and intestinal infarcts when anaphylactic shock was produced in animals. Watanabe (82) also Watanabe and Hosoya (83) demonstrated a marked reduction in the histimine content of the various tissues after anaphylactic shock. Tinel et al (84) demonstrated a well marked increase in the gastric juice in dogs with anaphylactic shock and attributed the shock to histamine release. Bartosch, Feldberg and Nagel (85) have shown that a histamine-like substance is liberated in the perfusate when isolated lungs are rendered anaphylactic by adding the antigen to the perfusion fluid. Several workers including Dzinich (86, 87) going on the theory that allergy is a sensitivity to histamine, desensitized allergic patients to histamine with very encouraging results. The Russian scientists have busied themselves with this phase of the subject in recent years. Wesselkin et al (88) claim that hemolytic shock resembles very closely histamine shock. They also claim to have substantiated the work of Hesse and Filatov in that renal spasm is part of the acute stage of shock from blood transfusion. Iljin (89) was able to demonstrate not only renal spasm as the result of hemolytic shock but azotemia as well.

It is probable that histamine release is the common denominator for a large number of apparently dissimilar conditions in which the shock syndrome is outstanding. A few more instances will be given. Stone (90) also Gerard (91) showed that the action of toxin taken from the gut above an obstruction and injected intravenously into another animal was almost identical

with histamine shock. Ellis (92) showed that the injection of a toxin similarly obtained into dogs with duodenal fistulae, renders the duodenal contents toxic to another animal almost immediately. This probably speaks for the release of a histamine like substance by the duodenal mucosa. Schloss (93) was able to isolate a histamine like substance from the intestinal contents of infants dying from obstruction. At this point it is well to again recall to the reader that all of these conditions in which histamine release appears to be the modus operandi also show an elevated blood urea; the one exception being food poisoning. This condition is however similar in all other respects, and an elevated blood urea will undoubtedly be revealed when more cases have been studied. The symptoms of food poisoning are similar to intestinal allergy and in several such cases there is an elevated urea N. (v. i.). One hears it frequently stated that the intestinal ulcerations seen in uremia are produced by the urea which is being excreted through the intestine, but from what has gone before it is apparent that these two conditions are both secondary to another underlying condition probably histamine release.

ALLERGY, UREMIA, AND GLOMERULONEPHRITIS

In the following instances gastro-intestinal symptoms and uremia occurred under circumstances that suggest an allergic basis. The first two cases suggest some form of intestinal or food allergy.

Case 9. A male 66 years of age developed acute abdominal pain after eating canned apples that he found on the city dump. This was followed by vomiting the next day, which continued for 4 or 5 days during which time there were no bowel movements. The pulse was 112 and the white count 6,400. The abdomen was quiet with rigidity, pain and tenderness. The blood pressure was 190 mm. of Hg. systolic and 118 diastolic, the Widal test as well as the urine were negative. After a few days, he had several normal bowel movements and he improved. Ten days after admission he developed pain in the abdomen again and some distension with rigidity. The urine now showed a specific gravity of 1008, contained a large amount of albumin with numerous red and white blood cells and granular casts. A few days later he became dyspneic, irrational and weak; his pulse became feeble, his temperature subnormal and the blood N. P. N. was 120 mg. per cent. He died in uremia.

Comment: The symptoms in this case were closely related to food taking and started with vomiting followed by ileus. The white count was rather low. This picture fits in quite well with a sensitivity or allergy. A cyclic response with an immediate and late reaction is typical in allergic conditions (v.i.). It is possible that the terminal state was an acute glomerulonephritis, the findings in the urine and the uremia would speak for it. The late time interval would put it in the period of antibody building—a close parallel to post scarlatinal nephritis. Also in hemolytic shock an early and late reaction is quite typical (v.s.). Barnes has shown that the same holds true for the shock syndrome following burns.

The next case also demonstrates an acute uremia under circumstances suggestive of food allergy:

Case 10. A middle aged man was brought to the hospital because of vomiting. His symptoms started after a party when he ate heavily of foods that he ordinarily was not accustomed to. The vomiting was followed by anuria with severe azotemia with very high values both for urea and creatinine. He died shortly afterward.

Comment: In this case the first phase of the reaction was so severe that the patient died in it. The patient related his illness to the meal that he had eaten and food allergy is suggested. The clinical picture resembles anaphylactic or hemolytic shock very closely.

The next case was reported by Motley (94) as periarteritis nodosa:

Case 11. A male 31 years of age who had suffered with asthma for 5 months began to notice fever, abdominal pain and bloody diarrhea. A biopsy of a piece of skin showed the typical picture of periarteritis nodosa. There was an eosinophilia of 87 per cent and the blood nitrogen reached 100 mg. per cent.

Comment: The allergic nature of the azotemia in this case is strongly suggested by the history of asthma and the eosinophilia. That periarteritis nodosa is an allergic reaction is believed by Rössle, Jaffe, and many others.

In another case where the patient was sensitive to wheat, a coincident rise of the blood nitrogen and a marked rise in the eosinophile count was observed. Hisanobu (95) has demonstrated experimentally that a rise in the urea nitrogen is associated with anaphylactic shock.

The allergic nature of acute glomerulonephritis was suggested by Schick as early as 1907. He observed that scarlatinal nephritis appeared during the period of antibody building and considered it an allergic reaction. Recently, experimental nephritis was produced by Masugi (96, 97, 98) with the use of allergins and confirmed by Arnott et al (99). The work of King and Finner (100) is also along the same line.

THE ROLE OF THE LIVER IN UREMIA

The frequent association of liver injury and uremia has been referred to in the literature from time to time. Faltitscheck and Hess (101) state that liver injury causes a disturbance of water exchange and that in acute atrophy of the liver a typical symptom is oliguria and anuria. They assume that the liver influences the water economy by a hormone action on the kidney. Boyce and McFetridge (102) in discussing a post operative liver-kidney syndrome believe that in liver injury the toxins cannot be detoxified and an extra load is thrown on the kidneys which soon break down and a lethal toxemia results. Hammerschlag claims very good results with liver injections in cases of uremia. He has divided the cases that benefit from such therapy into 5 groups, which makes apparent the association of liver injury and azotemia. They are as follows:

Group 1. Liver disease, jaundice, diabetes, increased N. P. N. and coma.

Group 2. Gastric tetany with duodenal ulcer, hypochloremia and uremia.

Group 3. Acute gastro enteritis, coma with no uremia or hypochloremia.

Group 4. Gastro enteritis, jaundice, stupor, uremia with normal chloremia.

Group 5. Empyema of the gall bladder with coma.

Eppinger et al claim that gall bladder edema is seen in uremia, eclampsia, severe burns and in hypersensitivity.

Nonnenbruch (103) claims that liver disease is re-

sponsible for a certain type of nitrogen retention which may be recognized by a partition of the nitrogen bodies in the blood. He claims there are 3 groups of nitrogen retention:

1. Increased urea and a normal non urea "rest nitrogen." This is seen in decreased concentrating ability of the kidney for urea, also in renal insufficiency, in extrarenal oliguria and in circulatory illnesses with water retention.

2. This group is characterized by a decrease in the urea and a rise in the non urea "rest nitrogen." It is not an expression of an excretory disturbance but a disturbance of the intermediate protein metabolism and is found in liver disease.

3. The second group may go over into severe renal insufficiency in which case the urea as well as the non urea "rest nitrogen" are elevated.

In the last year I have seen a case of liver necrosis, sepsis, with high values for both urea and creatinine, but with normal kidneys except for a few abscesses. Lichtman and Shoval (4) state that there is no evidence for the existence of a specific relation between the disturbance in the liver and renal manifestations and advise the term "hepatorenal" be dropped. They also state: "Similar renal changes and renal functional disorders have been noted in ileus, intestinal intoxication of infants, and diabetic acidosis. The primary factor is accepted to be extra-renal." Sutton (104) in discussing the "post operative high temperature liver death syndrome," states that the clinical picture resembles that seen in burns and in intestinal obstruction and that liver necrosis is observed in all of these conditions.

DISCUSSION

A critical review of the uremia cases cited in this paper reveals beyond very much doubt, that uremia cannot always be explained by a structural lesion in the kidneys. In addition, such factors as hypochloremia, acidosis, alkalosis, etc., can frequently be excluded as the cause. It is therefore proposed that there is a form of uremia which is of the nature of a "hypersensitivity" or "allergy," and that histamine release is in some peculiar way associated as the modus operandi. That such cases of uremia may rest on an antigen-antibody reaction is also a possibility. It has been shown quite definitely that histamine release depends on an antigen-antibody reaction by the work of Tinel et al (84) and Bartosch et al (85). In anaphylaxis, the resulting shock is also most probably due to histamine release; and according to Dale, anaphylactic shock is an antigen-antibody reaction. However, many allergists especially in this country do not believe that the antigen-antibody reaction is the "sine qua non" for allergy. For want of space this subject will not be pursued any further.

Exclusive of allergic reactions, there are several other possibilities for histamine release:

1. Trauma to the tissues might release the histamine contained in them as:

A. In burns it may be released from the skin.

B. Traumatic shock may be on the same basis.

2. Loeper et al (79) think that histamine may be released in protein metabolism.

3. Saylor and Wright (105) have demonstrated in a patient with urticaria that cold applications to the skin would produce the urticaria and an increased gastric acidity which they attributed to histamine release.

The cyclic type of reaction is not new in allergic thought, indeed it adds some weight to the belief that in uremia we are dealing with a type of allergy. In serum shock and serum sickness, we have examples of the early and late reactions to injections of horse serum. The cyclic reaction after blood transfusion has been well described by Bordley. The first phase is featured by hemoglobinuria and oliguria, the final phase by anuria, uremia and death. Recently Waldbott (106) has drawn another parallel in early and late asthma. He found that in infants who had died in very early asthma, the pathologic findings resembled more closely "shock" than they did chronic asthma. Tezner (107) claims that after intracutaneous skin injections, there are two skin reactions that differ as to time. There is an early one with wheal formation which goes away in an hour and a late one with tissue infiltration lasting several days.

SUMMARY

There are certain forms of uremia which depend on temporary functional changes of the kidneys, or to some cause entirely independent of the kidneys. For this type of uremia the term "extrarenal uremia" has been applied by some writers.

This uremia occurs under a wide variety of conditions. There is reason to believe that the uremia seen with hypochloremia, intestinal obstruction, acidosis, alkalosis, hypohydration, adrenal insufficiency, anaphylaxis, hemolytic shock, acute pancreatitis, etc., are all "extrarenal."

Shock is such a frequent accompaniment of the extrarenal uremia syndrome, that it is offered as the explanation for the sudden quick death observed in some of these patients.

Because of the close similarity between extrarenal uremia and anaphylactic shock and also because it occurs in situations suggestive of allergy, the idea is suggested that extrarenal uremia is a form of "hypersensitivity" or "allergy."

Histamine release or some related substance, should be considered as a possible modus operandi in many of the apparently dissimilar conditions exhibiting extrarenal uremia.

The evidence that extrarenal uremia rests on a hypersensitivity is not equally clear in all instances. In ileus, anaphylaxis, hemolytic shock, the hepatorenal syndrome and intestinal allergy we are probably dealing with a sensitivity; but in hypochloremia and adrenal insufficiency the evidence is not so clear because we cannot evaluate the factor of salt depletion at the present time. That salt poverty resulting from salt withdrawal can cause uremia in the presence of normal kidneys has been demonstrated experimentally; however, there is some evidence that the "withdrawal symptoms" in themselves are the manifestation of a sensitivity. In alkalosis, pancreatitis and intestinal intoxication, sensitivity or histamine release is suggested.

CONCLUSION

After reading this paper there are many questions that arise in one's mind which must remain unanswered. It is also apparent that the nature of uremia is exceedingly complex. Despite the fact that much space has been allotted to this subject, much

material had to be omitted and several important subjects had to be withheld or passed over with a sentence or two. Some of this material will be published in another article on treatment, but it is hoped that others will take up this important subject and discuss the many angles that remain. The importance of a review such as this lies in focusing attention on an important disease entity which at present is either overlooked or misunderstood. Undoubtedly, some of the theories developed herein will later be modified or found unsound but if discussion is stimulated, much will have been achieved. Despite the great contribution of Richard Bright to medical learning, nevertheless, it is true of him as of most outstanding personalities of the past in the field of science, their ideas and influence extend to a time when those ideas have become outworn. We have lived too long in the era of Bright; the light is seen in a different direction; and it is there that we must turn for the newer knowledge.

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Observations on the Nature of Heartburn*

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INTRODUCTORY REVIEW

OF the many symptoms of disorder along the gastro-enteric tract of which a great deal has been written and only little definitely known, heartburn certainly ranks high. It is commonly met with in disorders of the esophagus, stomach, duodenum, biliary tract and even of the large bowel. Frequently the only explanation to be found for its presence is a neurotic temperament.

Because its cause is still not clearly understood, a review of the more important literature may be helpful. One group of writers lay especial stress on presumed changes in the esophagus. In 1926, Jones and Richardson (12) distended the esophagus in 29 normal subjects with a balloon while watching with the fluoroscope. Nineteen of these people noticed a hot, burning sensation during distension of the lower third of the tube while the rest had only a sense of fullness or pressure. Distension of the middle or upper third of the esophagus caused a pressure sensation in twenty-five and burning in only four. Introduction into the lower third of the esophagus, through a tube, of small quantities of acid, alkali, cold water, gastric contents or barium suspension caused heartburn in two-thirds of those experimented upon. These workers also fluoroscoped their subjects as barium was given and found spasm at the level where the fluid had been introduced, with reverse peristalsis above. The spasm and reverse peristalsis persisted as long as did the heartburn. The conclusions were that heartburn is probably analogous to referred pain due to hunger contractions and is associated with a reflex disturbance of lower esophageal tone; or with abnormal peristalsis occasioned either by local disease or by functional or organic disease elsewhere in the body.

In 1931, Bloomfield and Polland (5) repeated this work with different results. They found that no matter at what point along the esophagus a balloon was placed, the majority of persons felt pain over the suprasternal notch or the lower sternum; that the sensations experienced were usually vague and widespread around a center, and that the site of pain bore no definite relation to the site of the stimulus. Only a few of the subjects complained of heartburn during the experiment. Bloomfield and Polland felt that this burning sensation might be due to spasm of the esophagus, and not necessarily to back flow of acid into the esophagus which occurs in many instances.

Bartlakowsky (4), who suffered with severe heartburn, was of the opinion that the presence of ectopic gastric tissue in the esophagus gave rise to heartburn. Basing his opinion on certain autopsy findings in children, he concluded that 70% of people have ectopic gastric glands chiefly in that part of the esophagus about the level of the thyroid gland. Kaufman, cited by Lewin (15), believed that the burning occurs because of an insufficient "slime" production by the esophagus which thus becomes more susceptible to irritation by gastric contents.

Barsony and Szemzo (2), studied thirteen patients after injections of barium suspension either with dilute hydrochloric acid or N/20 sodium hydroxide solution. They found that the hydrochloric acid would not cause burning in every case; that in two patients it actually caused the heartburn to disappear, and that sometimes the rapid injection of the dilute solution of sodium hydroxide gave rise to a burning more severe than that produced by the acid. They felt that esophageal tension with compression of the nerve endings in the wall played the chief part in the etiology of heartburn. From their experience and that of Schur, whom they cite as having allowed patients to *drink dilute hydrochloric acid without producing* heartburn, they doubted the importance of the acid factor in the production of this symptom.

Payne and Poulton (19), concluded that heartburn is associated with peristaltic movements of the esophagus and often with a rise in the mean pressure. In their opinion, heartburn is associated either with tonic contractions, or with alternating contractions and relaxations of the esophageal muscle. In their second paper (18) these investigators stated that esophageal pain or heartburn results from the stretching and deformity of sensory nerve endings in the wall of the tube. Hurst's (10) experiments in 1911 indicated earlier that distension was the important stimulus in the esophagus.

Bartels (3), in eighty-two post mortem studies of acute ulcerative esophagitis found varying degrees of inflammation which he felt probably explained the heartburn complained of by some of the patients before death. The lesions were probably terminal and due to the erosive action of gastric juice that was being vomited. That this is probably the explanation was shown by the work of Weiss and Mallory (23).

Hartmann's (9) solitary but very important case discounts the importance of the stomach and its acid juice in the production of heartburn. In 1921 he reported a case in which the stomach had been completely excised for a carcinomatous ulcer at the cardia. The jejunum was joined to the esophagus, yet the patient complained of heartburn. X-ray studies of the jejuno-esophageal juncture were negative on two occasions. Einhorn (8) doubted the influence of acid gastric juice in the causation of heartburn.

Most of the writers on the subject have been inclined to lay stress on a *combination of gastric and esophageal factors* (6). In 1884 Reichman (21) performed some important experiments which are now often forgotten. He tied small gelatin-coated sponges

*Work done at Guy's Hospital, London, under the direction of Sir Arthur Hurst.

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on a string and allowed them to pass down into the lower esophagus where they were left until the patients experienced heartburn and on pulling them out he found that only those from persons who had complained of heartburn contained fluid that gave an acid reaction. Another factor, he thought, was the opening of the cardia. This was caused apparently by contraction of the stomach, and his belief was that the degree of this contraction determined whether or not a patient had simple heartburn or heartburn with acid regurgitation. The cardia opened, he believed, because of the contraction of the stomach and because of reflex action started by alcohol, fatty foods or sauces in the gastric contents.

Hurst in his early work discovered that burning similar to that in heartburn could be caused by ordinary alcohol. In 1929 he suspected that there were two different types of heartburn. One came with acute indigestion and probably arose from fermentation, with possibly the production of alcohol or organic acid. Patients with this type were relieved by vomiting but not so well by the taking of alkalis. The second type was found in chronic dyspepsia with hyperchlorhydria and he thought it was due to tension on the muscle coats of the stomach.

Lewin (15), Lukacs (16) and Hugo Schmidt (22), all looked on the gastric and esophageal factors as intimately related. Briefly, their idea was that irritating gastric juice is thrown up into the lower part of the esophagus by a contraction of the stomach associated with an opening of the cardia; that the esophageal mucosa is thereby irritated and that this irritation expresses itself in heartburn of varying degrees of intensity. Schmidt suggested, on the basis of this theory, a form of treatment in which the fluid intake is lowered so as to keep the gastric contents thick and heavy so that they cannot easily run upward.

Lukacs (16) and Kauders and Porges (13) were quite sure that heartburn never occurred where real anacidity was present. They explained away exceptions by assuming that in such cases the anacidity after a test breakfast was not genuine and that more acid would be formed in response to a mixed meal.

Lukacs (16) expected to find two factors in the etiology, one an irritant and the other a hypersensitiveness. Porges and Sternberg (20), concluded that heartburn is brought on by an abnormal gastric motility, or contraction, associated with pyloric spasm, the gastric contents thus being pushed up into and irritating the esophagus. Crohn (7) was of the same opinion.

Winkelstein (24) in 1935 described a hitherto unknown abnormality which he felt explained heartburn in his cases. Five patients were examined by esophagoscopy because of recent complaints localizing trouble in the esophagus. Three had duodenal ulcers and another had a gastric ulcer. In addition, there was evidence, confirmed by biopsy, of acute or chronic inflammation in the lower third of the esophagus. Winkelstein explained this by assuming regurgitation of acid and pepsin into the lower esophagus, and retention of these substances because of spasm of the cardia. He thought the patient might be predisposed to this reaction by an "ulcer constitution." He found no evidence of ectopic gastric glands.

In addition to the two theories noted above, namely the esophageal and the gastro-esophageal, there remains a consideration of the *neurotic* factor in heartburn. Many writers describe it as a very important feature and Lukacs (16) especially pointed out how frequently a sudden change in milieu or a happier domestic or business situation cleared up the trouble. Finally, Kofler (14), in 1928 cured several cases of heartburn by removing their *infected tonsils* and felt that their trouble was due either to absorption of toxic material with a resultant vagus neuritis or to direct injury by swallowed septic matter.

RESULTS OF EXPERIMENTS CARRIED OUT BY THE AUTHOR

In five persons complaining of heartburn and six with achalasia of the cardia (cardiospasm), the following procedures were carried out:

1. A history was taken.
2. Gastric analysis was made before and after the giving of a test meal.
3. The effect of fasting gastric juice was noted on the lower third of the esophagus.
4. The patient was given a meal which usually provoked heartburn.
5. This meal was aspirated as completely as possible and divided into three parts.

(a) One portion was injected into the patient's esophagus at various levels.

(b) A second portion was injected into the esophagus of a person without a tendency to heartburn.

(c) The remainder was submitted to fractional distillation to detect the presence of alcohol or organic acids.

6. There was injected into the lower esophagus small amounts of from 0.3 to 1% hydrochloric acid, acetic acid, lactic acid; sodium bicarbonate, also water and brandy.
7. Whenever possible the injections were made while the patient was being observed with the fluoroscope.
8. In cases of achalasia of the cardia, the esophagus was first washed and then injection was made of various acids, an alkali, and some brandy.

SUMMARY OF RESULTS

1. Two of the first five patients studied suffered from severe heartburn despite the presence of an achlorhydria.
2. Fasting gastric juice injected into the lower third of the esophagus caused burning in two cases.
3. Injection into the lower esophagus of a portion of the "provocative meal" produced no heartburn. Injection of this same material into the esophagus of normal persons caused slight burning in the throat of one.
4. Fractional distillation of the "provocative meal" showed no alcohol or organic acids were present.
5. Injection of acid and later alkali produced no burning in three cases. In one case the rapid injection under pressure of anything, even water or a saturated solution of sodium bicarbonate, produced intense burning. One patient complained of burning only when 6 c.c. of 1% hydrochloric acid, or 1% acetic acid was injected.
6. During fluoroscopic observation no evidence was obtained of any motor abnormality such as regurgitation of a thin barium mixture from the stomach into the esophagus. However, heartburn could not always be induced while the patients were thus being observed.

7. The injection of acid or alkali into the lower esophagus of six patients with achalasia of the cardia did not produce heartburn.

8. Brandy almost always produced burning when allowed to trickle over the lower esophagus.

CONCLUSIONS

1. Hydrochloric acid injected into the lower esophagus in strengths up to 1% did not regularly cause heartburn in patients with this complaint.

2. In one case in which it did, the *rapid* injection of water or a solution of sodium bicarbonate (under slight pressure) had the same effect. This suggested the possibility of a reverse motor disturbance set up by an irritating forceful injection, and was in harmony with Alvarez's (1) theory.

3. Neither alcohol nor fatty acid was found in the stomach contents of patients who suffered from heartburn even though the meal had just recently provoked heartburn.

4. Injection of this same "provocative meal" into the esophagus of a normal patient seldom produced any burning.

5. The type of esophagitis present in cases of achalasia of the cardia seldom favors the production of heartburn from injections of 0.3% hydrochloric, or acetic acid or dilute solutions of sodium bicarbonate.

6. Brandy almost always caused burning when it was allowed to trickle over the esophagus.

7. On the basis of this preliminary study, and the work of Alvarez, Jones and Richardson, and Payne and Poulton, it appears that in some cases a reversed or a spastic motor activity in the esophagus is associated with heartburn.

ACKNOWLEDGEMENT

I wish to express my gratitude to Sir Arthur Hurst for his valuable advice and helpful suggestions.

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Editorials

EDITORIAL NOTE

The two papers in this issue by Drs. Verzár and Wilhelmj, Finegan and Hill, are the first to be published of a series solicited by the editors from directors of laboratories where work is being done of great interest to gastro-enterologists. It is to be hoped that each year these directors will send a brief resume of work done by them and their associates so that the readers of this Journal can keep closely in touch with what is being done on the firing line of research.

TEST MEALS AND METHODS OF GASTRIC ANALYSIS

THE study of the gastric secretory curve following administration of a test meal, once heralded as an important diagnostic procedure, is gradually falling into disrepute. Many clinicians believe that its only function is to show whether or not the stomach is capable of secreting acid and for this purpose histamine is gradually replacing the test meal. This change in attitude is in reality an expression of dissatisfaction with the methods and test meals commonly employed. A critical study of the usual methods reveals certain grave errors and points the way for improvements which may greatly increase the value of gastric analysis.

The commonly used clinical test meals (dry toast, bread, shredded wheat biscuit or arrow root cookies with water or weak tea) are unsatisfactory because of their low secretogogue content. This generally admitted deficiency has lead to the widespread use of *histamine*, the *alcohol test meal* and, especially in experimental work, the *ground meat and water test meal*. None of these test substances are entirely satisfactory as the following analysis will show.

Histamine is probably the most powerful stimulus for acid secretion known but this fact limits its field of usefulness, in that it commonly overpowers those regulatory mechanisms which normally lower gastric acidity. It is also said to stimulate only the acid and not the non-acid secretions of the stomach. For these reasons histamine should be used only to make sure that the stomach is quite unable to secrete acid; no other conclusions should be drawn from the test, and it should not be used when the investigator wishes to learn something of the *normal regulatory mechanisms*.

The *alcohol test meal* has no physiological justification and should be discontinued, since the response to it is probably a response to irritation of the mucosa. The *meat and water test meal* is theoretically ideal since it supplies commonly used secretaogogues in a normal manner, but due to the digestion of the meat and the use of phenolphthalein as an indicator in titration, the results are not only of doubtful value but probably are often grossly misleading. This can be shown in a striking manner by mixing finely ground meat with pepsin and hydrochloric acid until "free" acid is present and then titrating with N/10 sodium hydroxide, using phenolphthalein as an indicator. When this mixture is incubated at 37° C. it will be found that the titration values for "acid" increase rapidly and markedly and the so-called "free" acid disappears.

These changes are due to the liberation of protein digestion products which are amphoteric in nature and combine with NaOH as well as with acid. Hence, when this test meal is used, one is likely to titrate changes in the test meal, due to digestion, changes which may be large enough to overshadow those due to acid secretion by the stomach. This error has probably lead to much confusion in experimental work on animals.

Liebig's meat extract (Lemco brand) is a concentrated preparation of the secretogogues normally present in meat but it contains no protein. When a specially prepared 2 per cent solution is mixed with pepsin and hydrochloric acid and incubated at 37° C. the titration values (using brom-cresol purple as an indicator) remain unchanged. Liebig's extract thus possesses the advantages but not the disadvantages of meat. For this and other reasons it constitutes an ideal test meal.

A second grave error in the usual methods of gastric analysis arises through the failure of the laboratory worker to correct for the factor of dilution of the gastric secretions by the fluid of the test meal, originally pointed out by many continental workers, and later in this country by Gorham, (Jour. Am. Med. Assn. 1923, 81, 1738) and also through the failure to distinguish clearly between the acidity of the *gastric contents* and the acidity of the *gastric secretions* (Editorial, this Journal, Aug. 1937). These errors can be avoided by placing phenol red in the Liebig's extract test meal and determining the percentage of phenol red in each of the gastric samples withdrawn. The reduction in the percentage of phenol red enables one to calculate the volume of the secretions which have been mixed with each 100 cc. of the gastric contents.

Hollander has recently shown that the concentration of the acid secreted by the stomach remains constant (0.170 normal) regardless of the rate of secretion, and we have also shown that the concentration is unaltered by the degree of acidity of the gastric contents. Because of the constancy of the acid secretion one is able to separate the *total secretion* entering the stomach into two fractions, consisting of *the acid secretion* and the *non-acid secretions* and to study the changes in the amounts of each during the course of a fractional gastric analysis. In addition it is also possible to study the changes in the acidity of the total secretions entering the stomach.

A *third* error in the usual gastric analysis is the use of phenolphthalein as an indicator in the titration of total acid. In the presence of the organic material in the test meal phenolphthalein gives values which are very irregular and much too high when compared with the acid chloride in the gastric samples. This is apparently due to the fact that phenolphthalein combines with protein material. Hori (*Jap. Jour. Gastro-enterology*, 5, 13, 8, 1933), pointed out these errors and suggested the use of brom-thymol blue in place of phenolphthalein. We have found that titration with brom-cresol purple also gives figures in good agreement with the acid chloride values.

A *fourth* defect in the usual method of gastric analysis is the determination of the so-called "free" and "combined" acid. Both Martin (1934, 1, 330) and Hollander (1935, 2, 127) in this Journal, have criticized these nebulous concepts and suggested that the determinations be modified or discontinued. My associates and I have shown that sufficient information can be obtained from the measurement of the total acid alone and we have discontinued the determination of these doubtful entities.

In view of the above facts it appears that the value of gastric analysis could be greatly increased by introducing the following changes in technique: (1) The use of a suitable test meal such as that consisting of a specially prepared Liebig's extract solution. (2) Determination of the total secretions entering the stomach by adding phenol red to the test meal and determining the percentage of the original meal left in each gastric sample. (3) Titration of the total acid in the sample, using an indicator which is free from the errors inherent in the use of phenolphthalein. (4) The separation of the total secretions entering the stomach into the fluid of the acid secretion and the fluid of the non-acid secretions. (5) Determination of the acidity of the total fluid secretions entering the stomach. (6) Discarding the determination of what are known as "free" and "combined" acid fractions.

C. M. Wilhelmj, Omaha, Nebraska.

THE BACTERIAL FLORA OF THE GASTRO-INTESTINAL TRACT

ANY consideration of the bacterial population residing within the lumen of the alimentary tract should begin with the flora living on the lips. The junction zones where dry, stratified, squamous, epithelium joins with moistened mucous membranes are unusual bacteriological areas. The microbic inhabitants of such an area are different from those endogenous to the adjacent dry and moist surfaces. This is true for the lips, nares, anus, and external genitalia. This region of the lips has a very densely populated staphylococcus epidermic albus flora. These grow as very small, minute colonies, assume streptococci-like appearance on culture media. When the tip of the tongue moistens the lips there are many thousands of these cocci transferred to the oral cavity. The oral flora is seeded from the lips and the density of the oral flora is to a great extent dependent upon this habit of moistening the lips with the tongue. (Stuart, Knudson and Arnold, *Jour. of Dent. Research*, 15, No. 1:41, 1935).

The dorsum of the tongue supports a rich bacterial flora. Subcultures show active dissociation of this flora. Many types can be observed in smears that cannot be cultivated on any known media. Many pleomorphic forms can be grown for one generation only on artificial media. The dorsum of the tongue ranks next to mucosa of the colon in supporting a densely populated bacterial community.

The gingival margins of the gums allow a large number of bacteria to live on their surfaces. These are predominantly staphylococci in the healthy oral cavity.

The remaining surfaces within the oral cavity support a very scant bacterial flora, such as the cheeks, frenulum of tongue, etc., which are usually free of viable bacteria if the tongue is held stationary for ten minutes. These areas are seeded by the saliva due to lingual movement from the reservoirs of the lip and dorsum of the tongue. (Arnold and Stuart, *Amer. Jour. Digest. Dis. and Nutrit.*, II, No. 5:275, 1935).

Those areas supporting a densely populated endogenous flora also allow exogenous bacteria to survive longer than on other surfaces. Gulbrandsen and Keller (*Illinois Med. Jour.*, October, 1935), showed that tubercle bacilli remained viable on the lips for one hour and forty minutes. The epidemiology of enteric diseases can also be influenced by this long survival of exogenous bacteria on the lips and dorsum of the tongue.

Hood and Arnold (*Amer. Jour. Digest. Dis. and Nutrit.*, IV, No. 1:40, 1937), showed that exogenous bacteria in the oral cavity remained viable for two and a half hours, hence there was constant seeding of the stomach during this time by the swallowed saliva. The fate of the swallowed oral flora is dependent upon the acid-base equilibrium within the gastric lumen. So long as free hydrogen-ions are present within this cavity, few viable bacteria can be demonstrated. When the hydrogen-ion concentration is more alkaline than pH 3.0, the stomach becomes a reservoir for oral bacterial flora. The oral bacterial flora extends from the lips to the pylorus in subjects with an acid-deficient stomach. (Hood and Arnold, *Amer. Jour. Digest. Dis. and Nutrit.*, IV, No. 2:95, 1937).

The bacterial flora residing within the lumen of the duodenum and jejunum is dependent upon the physiological status of the stomach. This in turn is dependent upon the age of the individual and the diet. Arnold (*Jour. of Hygiene*, 29:82, 1929) concluded from animal experimental evidence that the flora of the upper half of the small intestine was dependent upon the acid-base equilibrium of the populum within this part of the alimentary tract. When there were a predominance of acid over alkaline reacting substances, then the flora was very scanty and consisted of only a few undifferentiated cocci, the so-called enterococci. When the contents were neutral or slightly alkaline, the bacterial flora was more complex and increased in density. Van der Ries (*Ergebn. d. inn. Med. u. Kinder.*, 27:77, 1925) observed a similar type of flora in the human under similar intro-intestinal acid-base balance conditions.

The reaction of the contents within the lumen of the duodenum is not the determining factor in the type or density of the bacterial flora residing within its lumen in so far as this may explain the bactericidal or growth inhibiting factors involved in this sparsely populated bacterial community. The mucosal functional activity seems to be the most important factor. If the gastric mucosal glandular action is normal, then the food ingested is saturated with acid radicals and becomes an acid buffered pabulum. When this passes into the duodenum the free acid is quickly neutralized, the combined acid is replaced by alkaline radicals more slowly. If, however, the material passed beyond the pylorus has not been fully saturated with hydrochloric acid, both physically and chemically, then the mucosal function of the upper intestinal tract does not react in the same manner as when the contents are fully and completely saturated with acid radicals. The control of the intra-intestinal bacterial flora of the duodenum and jejunum is dependent upon the mucosal activity of the lining of the alimentary tract from the gastric region downwards. When the contents of the duodenum and jejunum are found to range in the neighborhood of pH 5.0 to pH 6.5, then the bacterial flora only consist of a few (10 to 25) enterococci per cubic centimeter of contents. This indicates an excellent acidifying gastric mechanism. The gastric mucosal activity is inseparable from the duodenal mucosal function in respect to the control of the bacterial flora. The acid-base equilibrium of the contents of this part of the alimentary tract only indicates a balanced and a physiological function of the lining mucosa. The contents or extractable substances have little, if any, influence upon bacterial flora. Almost all common gastro-intestinal bacteria can grow *in vitro* in the environment of the normal intestinal contents. The determining factor is the physiological state of the mucous membrane lining the small intestine from the gastric region downwards.

The lower segments of the small intestine are usually considered along with this anatomical unit and have been thought to have, in general, the same physiological functions. The ileum is entirely different from the jejunum in respect to the bacterial flora residing within its lumen. There is a predominance of coliform types of flora. Many of these are slow lactose fermenters. There is some evidence of dissociation of bacteria within the lumen of the ileum. One should not forget the increase in lymphoid tissue beneath the mucosa and the accumulating evidence indicating an excretory function of this lower level of the small intestine.

Most of the information obtained upon the mechanism of the control of the bacterial flora within the lumen of the duodenum and jejunum has been based upon animal experiments. Anyone with experience realizes that these conclusions must be taken with some caution and reservation when applied directly to man.

The mechanism of control of the bacterial life residing in contact with the mucosa of the gastro-intestinal tract from the oral cavity to the lower level of the small intestine has been briefly reviewed. This summary was intended to stimuate gastro-enterologists to study these factors. The bacteriologist finds the alimentary tract a very complex and complicated environment for microbic life. The controlling mechanism of the gastric and small intestinal bacterial flora seems to be predominately of a biological nature. The intra-intestinal content has never been proven to contain the inhibiting or differentiating factors which act on the viable flora, endogenous and exogenous, to produce the microbic population usualy found within the lumen of this part of the alimentary tract. Extracts of the mucosa by various chemical processes have also failed to demonstrate a controlling factor, as a matter of fact such extracts stimulate growth of bacteria. Until we know more about these various factors controlling the composition and density of the bacterial population residing within the lumen of the stomach and small intestine, we might for purposes of convenience consider this a biological mechanism. The physiological process of hydrolysis of foods and absorption of the split products takes place in those parts of the small intestine which have about the same density of bacterial flora as the Sahara Desert has botanical flora.

Lloyd Arnold, Chicago, Ill.

Book Reviews

Les Abscès Du Foie. By P. Huard and J. Meyer-May. Paris, Masson et Cie., 1936. 390 pp., 98 figs., 65 French Francs.

THIS excellent exhaustive monograph on the liver abscesses is due to the observation of 174 cases at the school of medicine, Hanoi, French Indochine. 43 autopsies are reported. The content of the book is based not only upon the personal experience of the authors, but also upon an extensive knowledge of the international literature. The bibliography is excellent. The authors state that the multiplicity of the abscesses dominates the entire question, especially the therapy. It always should be tried to demonstrate everyone of the multiple abscesses. Therefore the importance of the radiologic diagnosis after injection of lipiodol is emphasized; because of the preponderance of multiple abscesses therapeutic puncture usually is not sufficient, and operation is to be preferred. The clinical part begins with extensive statistics. The chapter on etiology, and this perhaps is the most important contribution of the monograph, demonstrates that amebiasis, at least at Tonkin, plays but a small role as etiologic factor. In only seven cases amebiasis was found! In 27 cases another microorganism rather than ameba histolytica was found. The symptomatology is discussed thoroughly. The importance of systematic radiologic examination is emphasized; the use of artificial pneumoperitoneum is rejected, that of hepatography with thorium salts was not tried. X-ray examination using injection of lipiodol preceding operation or during operation is considered indispensable. The chapter on treatment is of special value because of the comparison of therapeutic procedures in various countries; one paragraph renders very well the situation in the United States following the epidemic of amebic dysentery; the experiences of the Mayo Clinic are quoted in detail. The medical treatment is discussed as far as amebic forms are concerned, especially the use of emetine although it is not considered as a specific drug; the effect of acetarsone, carbasone, etc., is mentioned, while yatren, vioform and the bismuth compounds are considered as valueless in amebic abscesses of the liver. The last chapter contains a detailed description of the operative procedures. The monograph can be highly recommended. It is astonishing that it was possible to write it under the special circumstances of a tropical colony.

Rudolf Schindler, Chicago, Ill.

The Avitaminoses. By Walter H. Eddy, Ph.D. and Gilbert Dalldorf, M.D.

THIS book is a sequel of the "Vitamin Manual" which the senior author published in 1923. Although the scope of this book includes both pathological and clinical discussions of the vitamin deficiency diseases, the authors state that they have planned to present a helpful manual rather than a complete treatise of the subject. In the opinion of the reviewer they have accomplished their purpose.

In Part I they discuss the nature and functions of vitamins, A, B, C, D, and E and devote chapters to the clinical, sub-clinical and anatomical manifestations of the several vitamin deficiencies. In addition there are well presented chapters discussing Beriberi and vitamin B; pellegra and vitamin G; scurvy and vitamin C; and rickets and vitamin D. Also there are chapters devoted to a discussion of vitamins in relation to resistance to infection, to morbid effects of complicated dietary experiments and to the relation between vitamins and blood regeneration.

In Part II there are three chapters devoted to discussion of the standard methods for bio-assay of the vitamins; various clinical tests for the estimation of vitamin C in the blood and other body fluids and a chapter devoted to the vitamin content of various foods.

The authors' index and subject index are satisfactorily complete and brought up to recent date.

Although there is much within the covers of this book that may be rather stiff reading and somewhat over the heads of casual readers, to those genuinely interested in this subject there will be found much of practical interest and importance.

B. B. Vincent Lyon, Philadelphia, Pa.

Abstracts

DONOVAN, EDWARD J.

Congenital Hypertrophic Pyloric Stenosis in Infancy. J. A. M. A., Vol. 109, pp. 555-561, Aug. 21, 1937.

Congenital hypertrophic pyloric stenosis is a condition which comes on early in infancy, usually between the second and fifth week after birth. The first symptom is vomiting which may, but usually does not, start abruptly. The vomitus is at first small in amount, but increases gradually and does not contain bile. This is persistent and results in rapid dehydration and loss of weight.

When the stomach is partially full, peristaltic waves may be visible. In addition to this, a pyloric tumor usually is palpable. The author believes this tumor to be pathognomonic of the condition.

Preoperative preparation is the all-important factor in surgical treatment of these conditions. There is no need to hurry operation. If the baby is in bad condition, he should be given one or two transfusions by the Lindenmann method. In addition, he should be given from 100 to 400 c.c. of normal saline by hypodermoclysis. The operation of choice is the Fredet-Rammstedt. It can be done easily, rapidly, and will give a permanent result.

In a series of 243 cases, the author has had only one death, with none in the last 143 cases.

Francis D. Murphy, Milwaukee.

HORSLEY, J. SHELTON.

"Emergency Surgery of the Stomach and Duodenum." South. Med. Jour., 30:549-553, May, 1937.

In a consideration of emergency surgery of the stomach and duodenum one must bear in mind the mimicry of symptoms offered by non-surgical conditions such as coronary thrombosis and pulmonary lesions as well as extragastric surgical diseases as cholecystitis, appendicitis, and acute pancreatitis. On the other hand while an external penetrating wound is obvious the possibility of serious damage to the stomach or duodenum by a blunt blow should be borne in mind.

Perforated peptic ulcers may not necessarily be preceded by gastric symptoms. Much confirmation of the diagnosis in suspected cases can be obtained by a flat X-ray plate showing gas under diaphragm. The operation should be as prompt and as simple as possible. The fluid in the peritoneal cavity should be aspirated, the perforation should be closed transversely by a few mattress sutures of fine chromic catgut, the adjacent peritoneal covered fat brought down against this suture line by another row of the same kind of sutures and no drain inserted except in cases of more than eight or ten hours duration. Decompression of the stomach by a Levine tube and intravenous dextros in Ringer's solution may be indicated.

Perforation of a malignant growth demands a partial gastrectomy even though accompaning mortality is high. Drainage both locally and in the pelvis should be employed in such cases.

Patients with perforations caused by shot, particularly bird shot, usually do better when treated expectantly with morphine and rest of the gastro-intestinal tract. This is true since the tiny wounds are usually effectively plugged by the mucosa.

Stab or bullet wounds as well as indirect trauma with symptoms of a rupture of the stomach or duodenum require immediate exploration, control of the bleeding and closure of the perforation.

In any operation on the stomach or duodenum low blood pressure readings indicative of shock call for intravenous dextros in Ringer's solution or blood transfusions.

Grossly infected abdominal wounds are best closed by the "open method" of H. C. Gamble, suturing the peritoneun securely but leaving the remainder of the wound as open as possible.

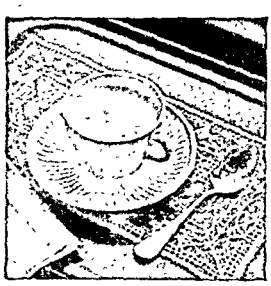
Gastric hemorrhage preceding operation can usually be controlled by medical measures but if too extensive or persistent resection of the involved area may be required.

Post-operative hemorrhage after gastric surgery is rather rare now. Careful technique and decompression afterwards through a Levine or Jutt tube are usually all that is necessary. If these measures and free irrigation of warm tap water or saline at about 120 degrees are not effective the bleeding point should be exposed and sutured through an exposure in the anterior gastric wall, care being taken not to disturb the sutures of the previous gastro-enterostomy or partial gastrectomy.

Failure of the stomach to empty after a gastro-enterostomy in rare and gastric lavage, for a few days will often give relief. If the obstructing exudate does not absorb laparotony with jejunostomy or more complicated procedures may be required.

The after-treatment of emergency gastric or duodenal operations consists of free use of intravenous dextrose and transfusions, physiological rest of the stomach, permission for water by mouth if a Levine tube is in the stomach, and a very gradual resumption of a smooth diet.

J. Duffy Hancock, Louisville.



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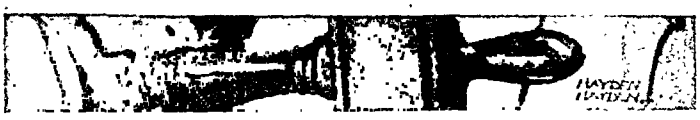
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All Red Cross services are supported by the annual membership dues of millions of Americans who join each year during the Roll Call, held from Armistice Day to Thanksgiving. Everyone is invited to have a part in the work of their Red Cross by enrolling in their local Chapter.

HELD, I. W. AND GOLDBLOOM, A. ALLEN.
Carcinoma of Stomach in a Cured Case of Addison's-Biermers (Pernicious) Anemia. J. A. M. A., Vol. 108, pp. 1398-1400, April 24, 1937.

The authors report a case of Addison-Biermer's anemia which was diagnosed and treated in 1927-1928. The patient was placed upon liver extract and diluted hydrochloric acid. The blood apparently returned to normal and the patient was considered one of those rare cases which was completely cured. In January, 1936, he returned with the complaint of loss of weight and appetite, weakness and occasional attacks of vomiting for the past six months. Physical examination and roentgen examination revealed a stomach mass which at operation proved to be a carcinoma of the pylorus. A gastric resection was done from which the patient apparently recovered.

Very few cases of this kind have been reported, and the author believes that when a recurrence of symptoms follows a cure of pernicious anemia gastric carcinoma must be thought of.

Francis D. Murphy, Milwaukee.

PAYNE, ROBERT L.
"Bile Tree Visualization — Its Surgical Importance." South. Med. Jour., 30:512-519, May, 1937.

Cholecystectomy alone in the presence of jaundice is an incomplete operation (except where acute cholecystitis is the cause of a hepatitis associated with a cholangetis) and the degree and type of common duct obstruction is often very difficult to determine clinically at operation even when a sound is passed into the duct and the ampulla is dilated. Furthermore, the status of the biliary tree post-operatively with a T-tube in the common duct can often be determined only inconclusively by the change in the degree of jaundice, stool examinations for bile, chemical and miscroscopical study of the external biliary drainage, and by irrigation through and by frequent clamping off the T-tube. For these reasons any procedure giving rather positive information regarding these conditions is of great value.

Such a method is used by Payne who follows the Mixter-Robins-Hermanson technic in his bile tract surgery. The procedure described in detail consists in the use of an opaque medium, hippuran, which may be injected into the common duct by a short shouldered angled No. 18 gauge needle during the operation, after aspirating the ductal system through the same needle, or may be injected through the T-tube post-operatively. One or more X-rays are taken after the injection to visualize the biliary tree. The use of hippuran appears to be harmless and properly interpreted plates reveal much positive information—not only regarding the degree or type of obstruction but also among other things even the reflux of bile into the pancreative duct.

Eight cases are described and illustrated with unusually good photographs. The method seems relatively simple and the results most convincing.

J. Duffy Hancock, Louisville.

KING, E. L., FAUST, ERNEST C. AND SANDERS, JOHN T.
"Intestinal Parasitic Infections Complicating Pregnancy." South. Med. Jour., 30:545-549, May, 1937.

Most readers, especially those not from the South, will be surprised at the incidence of intestinal parasites found in white pregnant women admitted to the New Orleans Charity Hospital. In a period of six and one-half years there were 3,290 cases admitted and 10 per cent were found to have *Endamoeba histolytica*, 5.6 per cent hookworm, 3.5 per cent ascaris, and varying percentages of the re-

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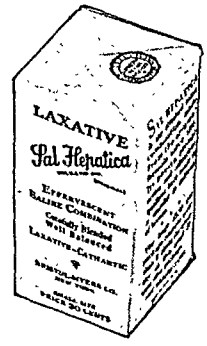
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latively harmless parasites — many of the patients having multiple infections. Had the number of stool examinations per patient been more adequate the incidence would probably have been even greater.

None of the patients with emabic infections presented any serious symptoms although approximately 50 per cent had diarrhea of variable intensity. Because of the short period of hospitalization only a few were treated, and the drugs most favored were chiniform, carbarsone, and vioform.

Hookworm infection is serious because of the frequency associated anemia, the latter condition resulting in a lowered resistance. Toxemia, abortion, fetal death and premature labor have been reported by other observers as showing an increased incidence in badly infected patients. The treatment used in the hookworm cases consisted of tetrachlorethylene in 3 c.c. doses given in hard gelatine capsules on an empty stomach, a saline purge being given the night before and two hours after administration of the drug. This course of treatment was repeated in some cases and in others additional medication for ascaris was given when indicated.

Ascariasis is ordinarily not serious but nausea and vomiting, intestinal discomfort, obstruction, perforation or peritonitis may develop. Treatment consisted in the administration of one gram of hexylresoricinol crystals in hard gelatin capsules on an empty stomach, followed by a saline purge and no food for five hours.

In none of the infected cases given treatment did abortion or premature labor occur — in fact it was believed that those complications were actually avoided by the eradication of the infection.

J. Duffy Hancock, Louisville.

BORAS, EDWIN.

Hay Fever and Asthma During and After Jaundice. J. A. M. A., Vol. 109, pp. 113-115, July 10, 1937.

Cincophen has been reported many times as the etiologic agent in disease of the liver. The author reports the case of a man, 36 years of age, who came to him complaining of jaundice of three weeks' duration. For the past eight years he had been suffering with hay fever, which affected him during the month of August. The entrance complaint was due to the taking of one hundred cincophen tablets over the course of ten months, for some rheumatic pains he had. It was noticed that with the appearance of the jaundice, both the hay fever and the rheumatic symptoms disappeared. After a stormy convalescence the jaundice disappeared and the patient made a complete recovery. The next summer he was observed for the development of asthma which did not occur despite deliberately living in a ragweed infested area. An intracutaneous test was done at this time, followed by a conjunctival test, both of which were positive although no constitutional symptoms developed.

Francis D. Murphy, Milwaukee.

MORRISON, LESTER M., SWALM, WM. A. AND JACKSON, CHEVALIER L.

Syndrome of Hypochronic Anemia, Achlorhydria and Atrophic Gastritis. J. A. M. A., Vol. 109, pp. 108-111, July 10, 1937.

In a review of four hundred gastroscopies, it was observed by the authors that a group of patients who had a hypochronic anemia and achlorhydria, had an atrophic gastritis, gastroscopically. The authors use the classification of atrophic gastritis adopted by Moutier, namely: diffuse and seg-



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mented chronic atrophic gastritis. These occur in three stages: (1) thinning out of mucosa; (2) effacement of gastric rugae; (3) arborization of the underlying and submucosal vessels.

The authors concisely discuss the opinions of various authorities on the etiology of the condition and believe, themselves, that it is the partial expression of a syndrome and not a disease entity. They conclude by saying that these cases will be studied during ensuing years, especially as regards the genesis of carcinoma of the stomach and esophagus, combined sclerosis of the cord and pernicious anemia.

Francis D. Murphy, Milwaukee.

LINDSAY, R. B., NEWMAN, J. R. AND HALL, I. C.

An Outbreak of Botulism in Wyoming. J. A. M. A., Vol. 108, pp. 1961-1964, June 5, 1937.

Cases of mushroom poisoning have frequently been reported, but only once has there been a report of botulism due to mushrooms.

The author reports an outbreak of botulism, type A, in a family eating home-canned mushrooms. Two children, aged two and one-half and five and one-half years, died because of respiratory paralysis before antitoxin could be administered. The mother and another child never showed any signs or symptoms of poisoning, but the father developed slight difficulty in swallowing during the second week, but recovered. These people received the antitoxin.

It was believed that the toxin of this strain was comparatively weak, but the culture showed a fairly patent strain of B. botulisms, type A.

Francis D. Murphy, Milwaukee.

APPENDICITIS

DAVIS, JAMES E., MUSKE, PAUL H., MULLIGAN, PHILLIP L. AND GUTOV, JULIUS.

A Statistical Survey of 10,000 Consecutive Cases at Providence Hospital. J. A. M. A., Vol. 108, pp. 1498-1500, May 1, 1937.

This is a survey of all the appendicitis cases occurring at Providence Hospital during the period from January, 1935, to May, 1935. More than 98 per cent of the cases were examined histopathologically. In 85.6 per cent of the cases clinically diagnosed as acute appendicitis, the diagnosis was confirmed pathologically.

There were 379 deaths in this series, of which 93 or 24.5 per cent were chronic; 257 or 67.8 per cent were acute; and 11.51 per cent were not classified. There were 6,076 females and 3,306 males in the group. There were more females because appendectomy was done in them in conjunction with other surgery. However, the mortality rate was higher in males because there were more acute, suppurative, gangrenous and ruptured appendices in this group.

The age of patients varied from ten months to 80 years. It was observed that the extremes of life produced 79.5 per cent of the total mortality, although 82.5 per cent of the cases were between the ages of 10 and 40 years.

The temperature on admission varied. Those with acute appendicitis had higher temperatures than the chronic cases had. Those which terminated fatally had temperatures ranging between 102 and 104 F.

EYERLY, JAMES B. AND BREUHAUS, HERBERT C.

Treatment of Ulcerative Colitis with Aluminum Hydroxide and Kaolin. J. A. M. A., Vol. 109, pp. 191-195, July 17, 1937.

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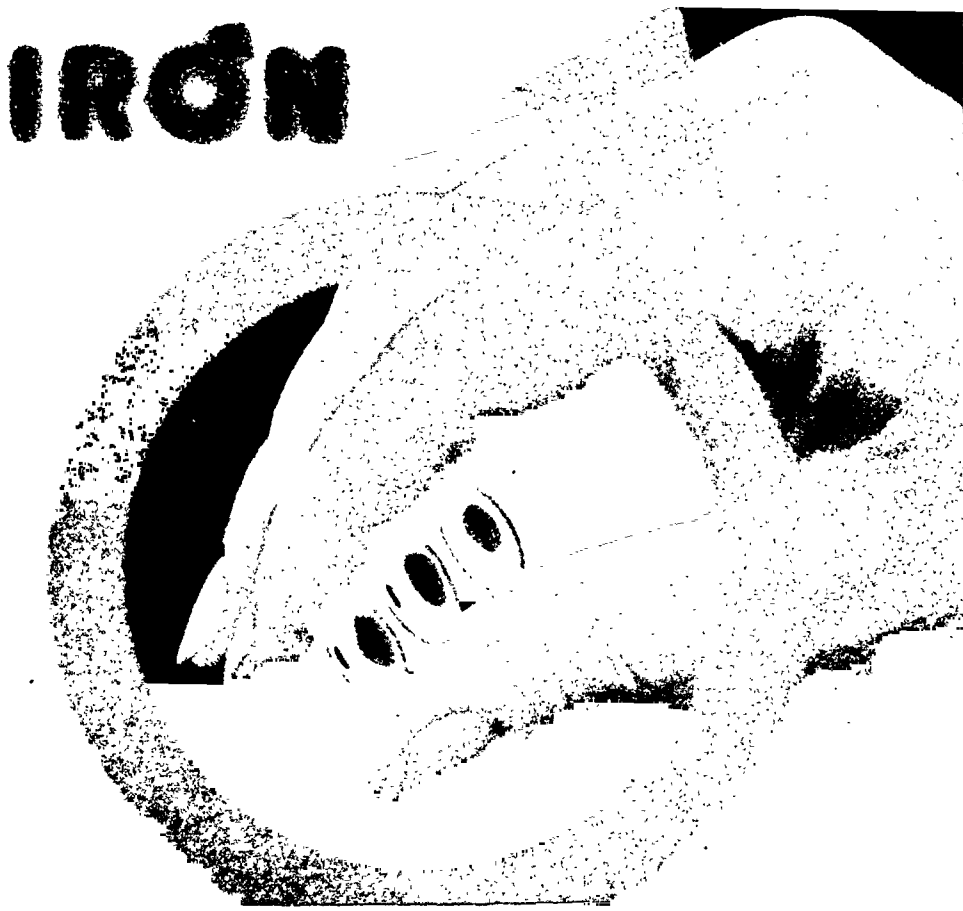
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man. It has been used successfully in the treatment of Asiatic Cholera. Its action is considered to be twofold: First, a mechanical action by which large numbers of bacilli are enclosed and carried off, but are not killed; second, the kaolin takes up toxins by adsorption.

Aluminum hydroxide is similar to kaolin, but has a greater colloidal activity, and also some astringent action. It also may act as a weak base or weak acid and has been used in the treatment of peptic ulcer. It has no demonstrable toxic effects when given orally, but has been known to cause a rapid drop in the red cells of two or three million when injected in large doses.

In the treatment of ulcerative colitis the author has used a mixture of three to five ounces of kaolin and aluminum hydroxide in three to five ounces of water given rectally once daily and retained as long as there is no discomfort. He has had excellent success in six cases and believes that it bears clinical trial.

Francis D. Murphy, Milwaukee.

KUNATH, CARL A.

The Stoneless Gall Bladder. J. A. M. A., Vol. 109, pp. 183-187, July 17, 1937.

The author has analyzed one hundred cases of noncalculous cholecystitis in which the gall bladder was removed. After comparing them with a similar series in which stones were present, he concludes that the stoneless cases show a greater morbidity, a higher postoperative mortality and only about half as many cures. He analyzed the stoneless cases from both the pathologic and the physiologic standpoint, but could find nothing indicative of the prognosis from either viewpoint. Generally, the more marked pathologic change present, the better the results. Colic was cured in eighty-six per cent of the cases, and dyspepsia in thirty-three per cent. Thirty-eight per cent of cases with no dyspepsia preoperatively complained of it postoperatively. He found some cases of poor results to be due to errors in diagnosis. These included cases of duodenal ulcer, duodenal diverticulum, a tuberculous spondylitis, chronic gonococcic peritonitis, and, in the majority of cases, gastro-intestinal nervous disturbances.

Francis D. Murphy, Milwaukee.

STEIN, J. J. AND HONTSCH, F. K.

Adenocarcinoma of the Rectum with Unusual Sites of Metastases. J. A. M. A., Vol. 108, pp. 1776, May 22, 1937.

There have been sixteen cases of adenocarcinoma of the rectum with metastasis to the liver reported. Many of these cases are characterized by priopism and the author believes that such a condition always should suggest the presence of some pelvic tumor. It is also believed that anatomically or physiologically such metastasis cannot be explained on a vascular or lymphatic basis. The author explains the metastasis by extension into the corpus cavernosum by way of the ischiorecta fossa and then through the junction of the deep and superficial triangular ligaments, with the fascia of Colles into the superficial perineal space. The author also reports a case with metastasis to the right leg and right foot.

Francis D. Murphy, Milwaukee.

CASE, JAMES L.

Comparison of Methods of Roentgen Examination of the Colon. J. A. M. A., Vol. 108, pp. 2028-2034, June 12, 1937.

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(1) 1935. The Lancet 228-I, 71
(2) 1936. Am J Med Sci., 191, 319
(3) 1935. Proc Soc Exper Biol & Med, 32, 1930
(4) 1933. J. Lab. & Clin. Med. 18, 484
(5) 1937. The Avitaminoses Eddy and Dahldorff William and Wilkins Baltimore
(6) 1936. J. Nutr. 12, 405
1936. Ibid. 11,383
1935. Am. J. Pub. Health 25, 1340

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meal with observation of the opaque residues as they move along the large bowel, followed by contrast enema administered under screen control by the radiologist himself with appropriate film records during the course of the fluoroscopy and subsequent observations after the patient has attempted to expel the contrast fluid. In anal insufficiency, the use of barium may be necessary even though the contrast clysma would be the method of preference. In cases in which there is a serious obstruction the use of umbrather in the oral contrast method may be desirable. The author believes that preliminary cleansing of fecal residues is ideal. He uses liquid petrolatum orally for one or two days or even 30 c.c. of castor oil the day before, followed by enemas the morning of examination. If an obstructive lesion, such as a carcinoma of the colon is suspected, the contrast enema is given first, followed later by air injection and stereoscopic films if necessary. In differentiating various types of colitis, the diagnosis of early carcinoma or the discovery of polyps and mucosal ulcerations, the double contrast method is of value.

Francis D. Murphy, Milwaukee.

LONG, CHARLES FRANCIS.

Leukocyte Behavior During Gastric Analysis. J. A. M. A., Vol. 109, pp. 23-25, July 3, 1937.

Kern was the first to suggest the fact that there might be some relationship between peptic ulcer and allergy; Vaughan's work indicated that there might be a relationship between leukopenia and food allergy. Gay believes that some cases of peptic ulcer may be associated with food sensitivity.

If some peptic ulcers were allergic manifestations, then, according to the author, some cases would certainly be found in a gastro-intestinal clinic such as his, using the Ewald test meal containing the most powerful allergens, milk and wheat.

In a series of 100 patients on whom 113 fractional gastric analyses were done and 678 leukocyte counts and differential counts, the following results were obtained. Thirteen showed achlorhydria, twelve showed hypochlorhydria, thirty-five showed euchlorhydria and forty showed hyperchlorhydria. The differential counts were of no significance. The leukocyte behavior showed that sixty-nine per cent fell into the indeterminate group. The author concludes that there is no actual relationship between the acid values and the leukocyte behavior.

Francis D. Murphy, Milwaukee.

FREIBERG, HENRY B.

Esophageal Stricture Dilated with Urologic Instruments. J. A. M. A., Vol. 108, pp. 1781-1783, May 22, 1937.

The treatment of esophageal strictures is primarily the domain of the otolaryngolotist. They usually occur following the swallowing of lye, corrosive materials and some poisons. As the stricture develops, the patient notices increasing difficulty in swallowing first of solid foods, and later even of liquid foods or fluids. This stricture can at first be dilated from above, but as the stricture advances, this becomes more difficult and finally impossible. Then a gastrostomy is done and the patient fed in this way. The author presents two cases of esophageal stricture in which retrograde bouginage through a gastrostomy wound was performed with satisfactory results.

Francis D. Murphy, Milwaukee.



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GROSS, H.

Sclerosis of the Hepatic Veins in Chronic Congestive Heart Failure. Arch. of Pathology, 23:4-457, April, 1937.

In a study of the inferior vena cava and the hepatic veins to their terminal branches in cases of chronic congestive heart failure due to various causes, the author found histologic changes comparable to those seen in arteries subjected to increased intra-vascular pressure. Macroscopically thickening of the intima with raised yellowish plaques were seen together with dilatation of the vessel and longitudinal fibrous streaks. The smaller the caliber of the vein the less marked was the fibrosis, but fibrous streaks were observed into the smaller branches. Microscopically the intima was found well preserved and usually markedly hypertrophied. This hypertrophy appeared roughly proportional to the degree of muscular hypertrophy of the media. The elastic tissue was also hypertrophied and especially was it marked in those veins in which the muscle elements of the media had suffered fragmentation and subsequent hyalinization and invasion of replacement connective tissue. This type of change was especially seen in cases of very long standing passive congestion. In cases of less duration the degree of muscular hypertrophy was very marked and oftentimes the outstanding feature of the picture. In places a localized accumulation of muscle cells on opposite sides of the vein greatly narrowed its lumen. Although yellowish plaques were found in some places these lesions were not marked by fatty changes and calcium deposition; this in contradistinction to the changes found in arteriosclerosis. The author believes these changes in the wall are essentially the result of increased intravascular pressure, that they are local in significance, largely compensatory in nature, and are not a part of a widespread vascular disease.

N. W. Jones, Portland.

CONNOTATIONS. By H. J. Sims, Denver, Colo.

Nephropexy was first performed by Hahn on April 10, 1881. Kuester, Esmarch and Delhaes each report having performed nephropexy in 1882. Kuester performed bilateral nephropexy in 1883. Weir was the first in America to successfully perform a nephropexy. Dowell of Galveston, was long credited with priority. Whether Dowell should receive this recognition may be judged by his case report. He passed a large needle threaded with a tape through the abdominal wall and the tumor. The ligature remained three months. Six months later an attempt was made to reintroduce the seton. The needle was broken and the broken end remained in the abdomen. At the end of two months the ligature was again successfully introduced. The patient was admitted to the State Lunatic Asylum in Austin, Texas, for two years. During this confinement the seton passed. Her condition improved and she was discharged from the institution. Two years later the kidney was removed.

Sonnenberg, in 1881, aware of unsuccessful autoplastic methods of repair of exstrophy of the bladder advocated extirpation of the bladder and union of the ureters to the urethal mucosa. Maydl suggested and Mikulicz attempted on two cases to transplant the ureters into the rectum. One patient died from chloroform poisoning and the other passed urine and feces involuntarily.

Causalgia, as a clinical entity, has been known since the days of 1864 when Weir Mitchell, Moorhouse and Keen first described the syndrome. It follows an injury and is characterized by severe constant and burning pain in the region supplied by one or more of the major nerves to an extremity.

Oppenheim, in 1899, was the first to recognize a hyphphyseal tumor with Roentgen evidence.

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Wutz, writing in 1883, denied that any large cyst of the urachus had been reported. He rejected all previous case records believing all reported cases represented either notable diagnostic errors or the description was so elusive to prevent classification.

Werth, in 1899, recommended enterostomy for relief of intestinal obstruction.

In 1890, Vanderveer was able to collect from the literature twenty-two cases of sarcoma of the bladder occurring in childhood.

The McBurney incision for appendectomy was described in 1894.

Gross, one of the ablest surgeons in the eighties, said, "The treatment of renal abscess must at first be strictly antiphlogistic and afterwards supporting."

Emil Bock, in 1880, described adenoma of the sebaceous glands.

In 1894, Gallup was able to collect sixty cases of fracture of the astragulces.

Twenty-seven years prior to 1877 only 150 excisions of the thyroid gland had been recorded.

A. C. Butler-Smythe, in 1897, was the author of a text book containing 119 pages. This book recorded all the ovariotomies done by the author—a series of 54 cases. He attributed his unusual success to abundant flushings of the peritoneal cavity with warm boiled water.

The treatment of exstrophy of the bladder previous to 1850 was mechanical. The object was to protect the bleeding mucous membrane and retain the urine. The first defined operative procedure was outlined by Roux, in 1852.



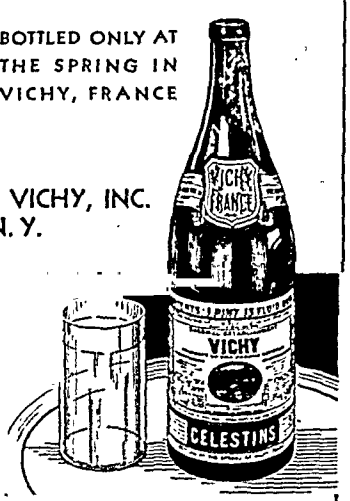
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GRAY, HOWARD K. AND KERNOHAN, JAMES W.

Meckel's Diverticulum Associated with Intussusception and Adenocarcinoma of Ectopic Gastric Mucosa. J. A. M. A., Vol. 108, pp. 1480-1483, May 1, 1937.

Meckel's diverticulum occurs in about 3 per cent of all individuals and benign ulcerating processes in ectopic gastric mucosa have also been described frequently, but the development of a malignancy in the ectopic gastric mucosa of a Meckel's diverticulum is extremely rare. The authors report the case of a woman who complained of vague abdominal pains of six years' duration. This was in the epigastrium in the lower abdomen, particularly on the right and in the lower back. Physical examination revealed a diastasis recti, slight tenderness over the right costal margin, and tenderness and a mass in the right lower quadrant. There was also an egg shaped mass in the ileocecal region. X-ray of the colon revealed a filling defect involving the ileocecal region. At operation an intussusception of the terminal portion of the ileum was found which, when reduced revealed another intussusception which appeared to be a large Meckel's diverticulum. A segmental resection of the ileum was performed by making an end to end anastomasis with an enteroanastomosis. The patient made a successful recovery and reported one year later that she was feeling fine, except for some slight discomfort in the right side at times. Microscopic examination of the diverticulum revealed that the mass within it was an adenocarcinoma.

Francis D. Murphy, Milwaukee.

BASSLER, ANTHONY.

Primary Suppurative Cholangeitis. J. A. M. A., Vol. 109, pp. 864-866, Sept. 11, 1937.

Suppurative cholangeitis is usually secondary to cholelithiasis, bile duct obstruction, parasites, carcinoma, and wasting conditions. The onset is insidious. It may begin as an acute catar-



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rhal jaundice. Pain is usually absent until late in the condition. The liver is diffusely enlarged and there is a polymorphonuclear leukocytosis. The diagnosis of the primary form is usually very difficult, but when it can be established as being secondary to something like gall stones, the diagnosis is fairly simple.

The author presents the case of a physician who presented himself with the complaint of jaundice of three weeks' duration. The illness began after an emotional shock and was characterized by jaundice, clay colored stools, bile stained urine, pruritus, anorexia, loss of weight and weakness. The temperature varied between 100 and 105, and there was a leukocytosis of 10,000 to 22,000. The comparison of the blood phosphatase and urobilinogus tests suggested involvement of some liver tissue.

Operation was performed, the gall bladder and bile ducts were examined and no stones were found. Choledochostomy was accomplished with a T tube, and cholecystogastrostomy was performed. A densely adherent appendix was removed. Microscopically, small sections of liver showed small foci of necrosis with polymorphonuclear infiltration. The wall of the gall bladder showed an active inflammatory process. After a very stormy convalescence, he recovered and is now back at work.

Francis D. Murphy, Milwaukee.

DAVID, VERNON C.

Chronic Intestinal Obstruction Due to Lesions of the Large Bowel. S. G. O., Vol. 64, No. 2A, pp. 281-285, Feb. 15, 1937.

Sub-acute and chronic obstruction of the large bowel is caused by cancer far more often than by any other disease. Diverticulitis and ulcerative colitis are next, while strictures, granulomatous lesions, and endometriosis and polypoid tumors are rare causes. Acute obstruction develops when any of those processes completely occludes the bowel or in other uncommon conditions, such as congenital atresia of the bowel, volvulus, intussusception or strangulation, as occurs in a sliding or diaphragmatic hernia.

The symptoms of chronic obstruction due to cancer may be so slight as to escape the notice of any but an alert patient.

After the point of obstruction has been determined a colostomy or cecostomy, proximal to that point, should be made as a preliminary operation. At that time the abdomen should be explored and the operability of the tumor determined. If it is found to be inoperable a short circuiting operation around the tumor may be made. The author warns against radical operations or even short-circuiting anastomoses in the presence of even a slight degree of obstruction.

When diet, belladonna, heat and rest do not relieve the obstruction due to the diverticulitis, colostomy may be necessary. After six to twelve months the colostomy may be closed if the diseased portion has returned to a fairly normal state.

Acquired strictures of the rectum caused by advanced lymphogranulomatosis inguinale is best treated by permanent left-sided colostomy.

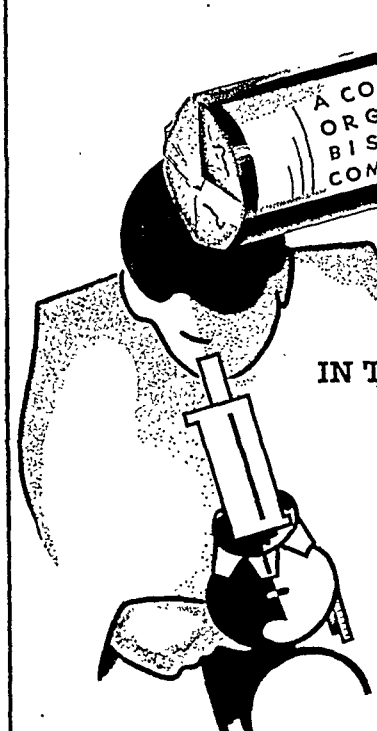
Rarely congenital strictures are not recognized in childhood and persist, causing megacolon in adults.

Six figures accompany the article.

HORSLEY, J. SHELTON.

Resection of the Rectosigmoid and Upper Rectum for Cancer with End-to-End Union. S. G. O., Vol. 64, No. 2A, pp. 313-321, Feb. 15, 1937.

The desirability of preserving the function of the rectum and anus in the treatment of cancer of the recto-sigmoid and upper rectum prompts the author to report a method of resection



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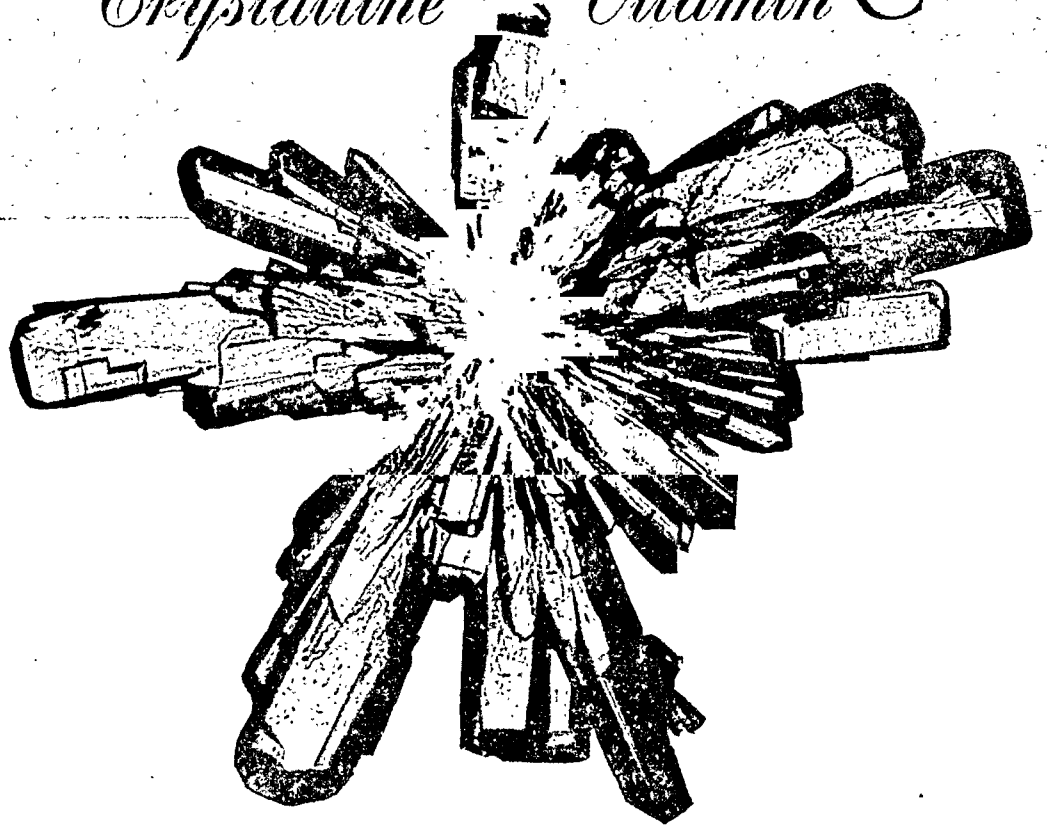
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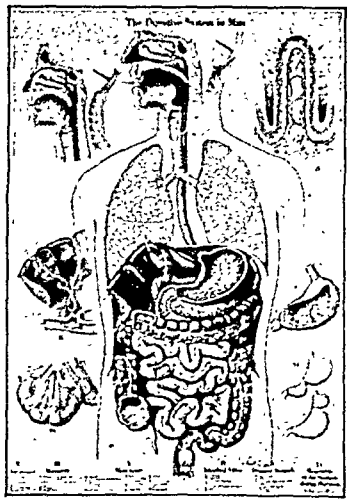
Such conditions may arise not only from an inadequate diet, but also from an inability to assimilate sufficient vitamin C from the diet. Vitamin C deficiency not infrequently results from the use of special diets, either self-imposed or prescribed.

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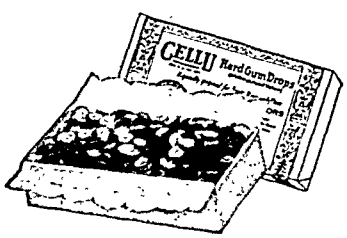
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of that part of the bowel with end-to-end union.

Since the spread of cancer of the recto-sigmoid and rectum is by way of the lymphatics and therefore mainly upward, it is not necessary to remove a large part of the bowel below the growth.

A preliminary cecostomy by means of which all fecal material is diverted from the distal colon is absolutely essential to the success of any end-to-end anastomosis in the colon. In order to secure this the author inserts a plug of vaseline gauze into the distal opening of the bowel through the opening in the cecum if it is necessary. The bowel is cleansed by irrigations from above and enemata from below. If, after the establishment of the cecostomy, there is a tendency to looseness of the bowels that must be controlled for several days before the resection is undertaken.

For the operation spinal anesthesia is preferable. The patient is grouped and a blood transfusion is given at the close of the operation, or later if it is deemed necessary. If the liver contains metastases which are not extensive and the lesion is obstructive in type, the resection is carried out as planned. If the tumor is found to extend too low to allow end-to-end union, the abdomino-perineal resection after the method of Miles, is carried out. The author has used Steinberg's colibactragen in all cases and believes it to be a distinct advantage.

After the operation enemata or irrigations of the large bowel should not be given. After two weeks the plug in the distal stoma of the cecostomy and what passes through is allowed to pass. Mineral oil is given in adequate amounts and a low residue diet is advised for at least a month after operation.

When it is evident that the colon has resumed its function, the cecostomy may be closed. The author inverts the mucosa of the cecum and finally frees the cecum from the parietal peritoneum and fixes it against the peritoneum above the incision, which is closed with catgut sutures. The remainder of the wound is packed open with vaseline gauze.

Three cases are reported in detail. Eleven figures accompany the article.

NOTICE

The 1938 meeting of the American Proctologic Society will be held at the St. Francis Hotel in San Francisco on Saturday, Sunday and Monday, June 11th, 12th and 13th, under the Presidency of Dr. H. Z. Hibshman of Philadelphia. Dr. Granville S. Hanes of Louisville, will deliver the first annual Joseph M. Matthews address.

Guests sponsored by members of the Society will be admitted to the sessions.

Curtice Rosser, Dallas.



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Containing coagulated whey proteins, there is less likelihood of allergens entering the blood stream of individuals sensitized to milk.

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WANGENSTEEN, OWEN H.

Rationalizing Treatment in Acute Intestinal Obstruction. S. G. O., Vol. 64, No. 2A, pp. 273-280, Feb. 15, 1937.

In a review of some the pathologist physiology of intesintal obstruction the author points out that the increased intraluminal pressure by compromising the blood supply of the bowel wall leads to tissue necrosis and perforation leading to transperitoneal absorption. The concept that a toxic substance is absorbed from the wall of the obstructed bowel has been discarded. Intraluminal pressure is reduced in high obstructions by reverse peristalsis which, with vomiting, reduces the mineral and fluid content of the patient so rapidly that death ensues from their insufficiency. Replacement of fluid and minerals prolongs life in cases of high intestinal obstruction. The important factor in the treatment of low intestinal obstruction is the reduction of intraluminal pressure before the bowel wall has been damaged.

The concurrent occurrence of intermittent cramp-like pain and borborygmus establishes the presence of intestinal colic. This, in the absence of enterocolitis and in combination with some degree of distension of the abdomen, establishes the presence of an intestinal obstruction.

Where this obstruction is due to volvulus, intussusception, or a strangulated hernia, the treatment is apparent. In certain other instances in which the required treatment is not so plainly indicated the author observes three essentials for the proper procedure. (1) The sterility of the peritoneal cavity must be preserved inviolate. (2) The operation of least magnitude which will undo the injurious effect of the obstruction be performed. (3) That immediate restoration of the continuity of the intestinal tract be a matter of secondary importance unless the resulting fistula would prove serious.

In certain simple obstructions in which the location of the block has been determined by X-ray, suction may be applied and its results followed carefully by frequent films of the abdomen. If the bowel is returning to normal state the treatment may be continued. This form of treatment should not be undertaken alone for low intestinal obstruction or for any occlusion of the large bowel. It is valuable only as a pre-operative procedure in those cases.

Four figures and a bibliography accompany the article.

NICKERSON, D. A. AND WILLIAMS, R. H.

Malignant Tumors of the Small Intestine. Amer. Jour. Path., XIII:1, 53, Jan., 1937.

The authors report 10 cases of primary neoplasm of the small intestine occurring in 11,206 autopsies performed in the Mallory Institute of Pathology during the past 40 years, and review briefly the literature on the subject. The 10 cases consisted of 2 leiomyosarcomas arising in the duodenum and 8 carcinomas, 6 of which occurred in the duodenum and 2 in the jejunum. The incidence of the latter to carcinoma of the intestinal canal in the series was 2.33 per cent.

Metastases, especially into the liver and the regional lymph nodes, occurred abundantly in 7 of the 8 cases of carcinoma. The 2 cases of sarcoma showed no secondary growths.

The symptoms and clinical findings are briefly summarized in the report and are of interest. Duration of symptoms before the patients entered the hospital was over 7 months. The clinical picture depended upon the site of the tumor, the type and grade and the presence of metastases. Bloating and epigastric pain after eating, sometimes vomiting or an acute attack of intestinal obstruction occurred. Weakness, loss of weight and strength, altered bowel function and progressive anemia were usually present. The roentgen ray findings in 4 of the 10 cases were dilatation of the stomach with gastric residue without demonstrable gastric lesions and distortion of the duodenum. All were diagnosed as extrinsic tumors or deformities due to adhesions.

N. W. Jones, Portland.

WILDER, RUSSEL M.

Clinical Investigations of Insulins with Prolonged Activity. Ann. Int. Med., Vol. 11 (O. S., Vol. XVI), July, 1937.

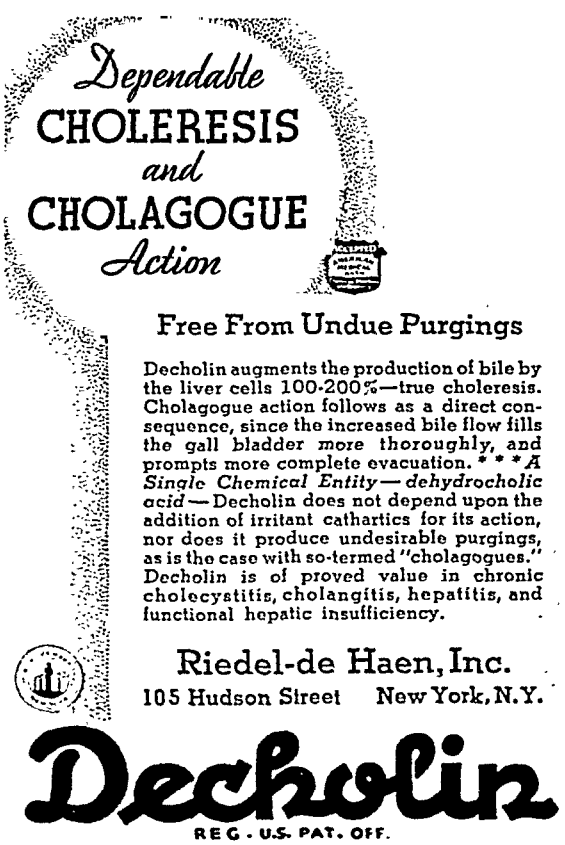
This is a very thorough study of the peculiarities of the action of insulins with prolonged activity, and their advantages in insulin hypersensitive diabetics of five years or longer.

The author presents case reports with charts illustrating: (1) the prolonged action of protamine insulin in comparison with the plain, calcium and zinc protamine; (2) studies of prolonged hypoglycemia; (3) the control of glycosuria by diet.

One dose of crystalline insulin (which is quicker acting) will not hold over twenty-four hours, so he recommends crystalline and protamine insulin given at the same time, administered in different syringes, as producing the most evenly balanced results.

An able discussion of protamine insulin to prevent protein waste, and in treatment of diabetic acidosis, completes this very worthy paper.

B. B. Vincent Lyon and Clifford H. Arnold, Philadelphia.



Vi-Syneral for Nutritional Deficiency Conditions



Restricted Diets

FACED with the necessity of removing offending foods from the dietary, the physician well recognizes the serious threat to general metabolism, particularly through the curtailment of the necessary vitamin and mineral intake.

In the case of the obese, or diabetic, a diet low in total calories — with a diminution in carbohydrates and a limitation of fats — inevitably presages a deficiency in most of the vitamins, especially A and D, and the minerals.

In renal disease, characterized by nitrogen retention, the physician must deprive the patient of the larger part of his normal protein consumption — even though he recognizes the concurrent loss, particularly, of vitamin B and many of the mineral elements.

For the gastric ulcer case, or for the patient with colitis with spastic colon, the blue pencil rigorously bars uncooked fruits, vegetables and salads — likely through contained roughage to irritate the gastrointestinal mucous membrane. With them go much of the patient's supply of vitamins A, B, C and E — as well as calcium, phosphorus, iron, etc. — since the vitamin potencies and mineral content of pureed vegetables and fruit juices inevitably suffer serious impairment.

Allergic patients present a particularly difficult problem . . . the foods responsible for the allergic symptoms usually being so important to the normal dietary.

Modern authorities on dietetics emphasize the imperativeness of ensuring an adequate supply of vitamins and mineral salts, and of maintaining a normal acid-base balance, in these restricted diets. Deficiencies are rarely singular, since most foods contain three or four vitamins and various minerals.

It ill suffices, therefore, to supplement the diet by single-vitamin concentrates or specific mineral salts. The interdependence of vitamins and minerals in normal metabolism, and the multiple deficiencies induced by elimination from the diet of any essential food, can be met adequately only by the employment of the original multiple vitamin-mineral concentrate, Vi-Syneral.

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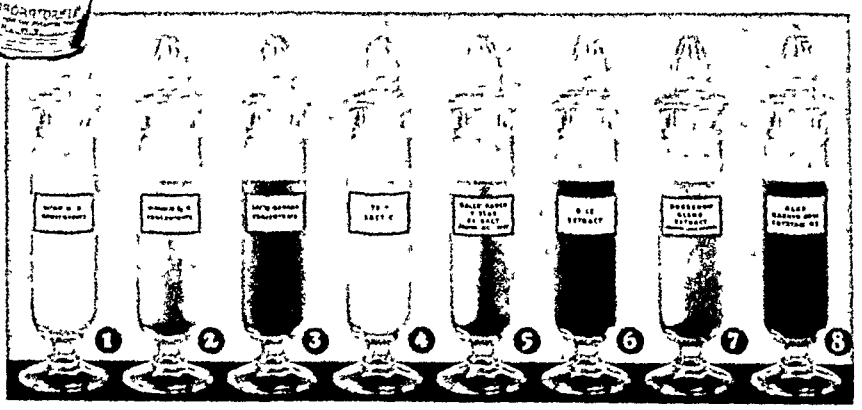
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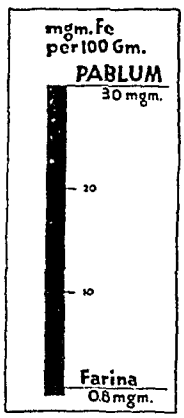
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The Influence of the Extrinsic Innervation on the Human Gastric Motor Mechanism

By

LOUIS E. BARRON, M.D.* (by invitation)
NEW HAVEN, CONNECTICUT

THE clinical results of bilateral resection of the splanchnic nerves have inspired new optimism in the treatment of essential hypertension (1) and juvenile diabetes (2, 3, 4). Although the therapeutic value of this procedure is still on trial, nevertheless it has created opportunities for investigating the role of these nerves in the body economy. Our own observations in this field became possible when bilateral resection of the splanchnic nerves was accomplished in an attempt to control juvenile diabetes (5). Further studies on the gastric neuromuscular mechanism were made when abdominal vagotomy was performed on a patient with vagotonia (6), a symptom-complex described by Eppinger and Hess (7). It thus became possible to make comparative studies on the influence of the extrinsic innervation on the motor physiology of the stomach.

METHOD OF INVESTIGATING GASTRIC MOTILITY

In the investigation of gastric motility we used the balloon and kymograph method. The details regarding the apparatus, the criteria for evaluating gastric activity, and the method for ascertaining the location of the balloon in the stomach have already been reported (5, 6). The usual duration of each continuous observation ranged between three and six hours. Observations were made in the morning about fourteen hours after the evening meal. As a preliminary procedure a barium coated balloon was swallowed and its position in the stomach verified by the fluoroscope and X-ray films. The distance from this position to the incisor teeth was measured and kept constant throughout the experiments. Because of the great variability in gastric motility a large number of control experiments were made to facilitate comparative study.

During the kymographic tracings an electric key and signal magnet were incorporated into the system. All patients were instructed to indicate any abdominal distress by pressing the key which produced an informative mark on the record. It then became possible to correlate gastric sensory disturbances with the associated phase of motility. All kymographic records were carefully evaluated and tabulated for comparative study (Table I).

Gastric motility was again studied from five to seven months after operation for the investigation of the late results.

Studies were also made on the influence of the extrinsic innervation on the emptying time of the human stomach. The patients were given a test meal consisting of three ounces of cream of wheat, two ounces of barium sulphate, and sufficient water to form a paste. Frequent fluoroscopic observations were made until barium was no longer evident in the stomach. Occasionally it was difficult to ascertain accurately when the stomach was empty due to the coating of the walls by barium. However this was not a constant artifact.

THE SPLANCHNIC INNERVATION OF THE STOMACH

The anatomical distribution of the splanchnic nerves has been reviewed adequately elsewhere (8, 9). Therefore further discussion is intentionally omitted.

Although numerous experimental observations have been made on the influence of the splanchnic nerves on gastric motility, nevertheless divergent results have been reported. Certain contributory factors such as anesthesia and trauma have frequently obscured the subsequent experimental conclusions.

In spite of this criticism there is sufficient evidence to indicate (10) that resection of the splanchnic nerves in dogs produced an increase in gastric tonus and an augmentation of the contractions. We have concluded from our own observations (5) that this was also true in man, since a marked increase in the duration of periods of gastric motility and a definite increase in the amplitude of the contractions were evident. This was thought to be due to the unopposed action of the vagus nerves.

Following bilateral splanchnic resection we observed great variability in gastric activity. Occasionally the motility was normal and resembled that noted during the control studies. Since the splanchnic nerves contain both motor and inhibitory fibers (11, 12), the results appearing on the kymographic tracings are influenced by the state of the gastric tonus existing at the time of the observation (13, 14, 15).

The immediate effect of splanchnic resection on the gastric motor mechanism was unreliable since the shock of operation, trauma, and anesthesia probably

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From the Department of Research Surgery, the Ohio State University, Columbus, Ohio.
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influenced the motility. Observations made eight to ten days after unilateral resection revealed very short periods of motility alternating with short periods of gastric quiescence. This was observed for about three to four days and was interpreted as being due to trauma and irritation to the sectioned splanchnic nerves. Subsequently there ensued intense persistent gastric activity. Frequently this continued throughout an observation period of four to five hours. There was a definite increase in the amplitude of the contractions which occasionally measured 14 cm. Many periods of motility terminated in severe gastric tetany. In spite of this increased activity there were no associated symptoms. There was no evidence of colic or diarrhea.

TABLE I

THE INFLUENCE OF THE EXTRINSIC INNERVATION ON GASTRIC MOTILITY

PATIENT	CASE NUMBER	DIAGNOSIS	METHOD OF STUDY	NUMBER OF CONTROL OBSERVATIONS	TREATMENT	NUMBER OF POST-OPERATIVE OBSERVATIONS	RESULTS					
							DURATION OF PERIODS OF QUIESCENCE	DURATION OF PERIODS OF ACTIVITY	CONTRACTIONS			
									NUMBER	DURATION	INTERVAL BETWEEN	AMPLITUDE
EF	345601	Diabetes	Balloon & Kymograph	15	Unilateral (left) Splanchnic Resection	21	Decreased	Increased	Increased	No change	No change	Increased
					Bilateral (right) Splanchnic Resection	25	No further change	No further change	No further change	No change	No change	No further change
					7 months after Bilateral Splanchnic Resection	9	No further change	No further change	No further change	No change	No change	No further change
MW	354581	Diabetes	Balloon & Kymograph	16	Unilateral (right) Splanchnic Resection	25	Decreased	Increased	Increased	No change	No change	Increased
					Bilateral (left) Splanchnic Resection	17	No further change	No further change	No further change	No change	No change	No further change
RM	350531	Vagotomy	Balloon & Kymograph	13	Atropine medication	9	Slight increase	Slight decrease	Slight decrease	No change	Slight increase	Slight decrease
					Vagotomy	12	Increased	Decreased	Decreased	No change	Increased	Decreased
					5 months after Vagotomy	7	No further change	No further change	No further change	No change	No further change	No further change

One patient was studied seven months after bilateral splanchnic resection (16). The results at this time revealed essentially no change in the motility. The increase in the duration of periods of gastric activity still persisted and lasted from three to four hours. The increase in the amplitude of the contractions was still evident, frequently ranging between 11 and 14 cm. (Figure 3).

Associated with these studies observations were made on the emptying time of the stomach (Table II). Five determinations were made during the control period. The results were fairly constant. The emptying time ranged from four hours and fifteen minutes to five hours and twenty-five minutes and averaged four hours and forty-five minutes.

Five observations were made after unilateral resection. There was practically no change in the average rate of gastric emptying when compared with the results of the control period. The total emptying time ranged from three hours and thirty-five minutes to six hours, and averaged four hours and forty-one minutes, an average difference of only four minutes.

Six observations made subsequent to bilateral splanchnic resection revealed a variation from two hours and forty-five minutes to four hours and fifteen minutes. The average emptying time was three hours and thirty minutes, an average difference of one hour and fifteen minutes.

Contrary to the findings of most observers, Cerqua (17) found that the stomach of most of his experimental animals appeared to be less active after splanchnic resection. However he was able to confirm the findings of McSwiney (18) in that the initial emptying after splanchnotomy was permanently shortened. He also noted a decrease in the total emptying time in some animals, but he did not think that this was permanent.

McCrea (19) found that splanchnotomy resulted in an increase in peristalsis. The stomach also appeared small and tubular. This effect gradually became less marked and it returned toward the normal state. Under these circumstances the initial emptying time remained markedly shortened while there was an appreciable decrease in the total emptying time. Our findings concur with those of McCrea (19) in that the rapid emptying seemed to be due to an increase

in the gastric activity rather than the result of a patulous pylorus.

THE VAGUS INNERVATION OF THE STOMACH

The abdominal distribution of the vagus nerves has already been described in detail (18, 19, 20). McCrea (19) has shown that each vagus sends fibers to both surfaces of the stomach and that stimulation of a single vagus in the neck will cause movements of the whole stomach. Resection of both vagi in the neck has proved fatal since esophageal and laryngeal paralysis results and death subsequently ensues from respiratory infection. Intrathoracic or abdominal vagotomy can be accomplished with a relative degree of safety.

It is believed that the gastro-intestinal manifestations of vagotonia are due to hyperirritability of the vagus nerves. Many of our observations are in keeping with this view. During the untreated stage of this condition intense gastric activity was a common observation (Figure 4). Associated with this there was a corresponding decrease in the duration of periods of gastric quiescence. By means of the signal magnet and electric key it was possible to correlate epigastric discomfort with the associated phase of gastric motility. Such a relationship was observed. During the control period severe contractions were noted occasionally of sufficient magnitude to rupture the balloon. These contractions occurred simultaneous with the upper abdominal distress. The amplitude of the contractions was increased, occasionally to 8 cm. Gastric tetany was common, and frequently was accompanied by temporary periods of discomfort which disappeared with the ensuing period of gastric quiescence. With the resumption of intense gastric motility there was a simultaneous recurrence of epigastric distress. In general there was a definite increase in gastric tonus as detected by the balloon method.

TABLE II

The influence of the extrinsic innervation on emptying time of the stomach

Patient	Case Number	Diagnosis	Emptying Time of the Stomach			
			Average Preoperative Emptying Time	Treatment	Average Postoperative Emptying Time	Difference
M. W.	354581	Diabetes	4 hours, 45 minutes	Unilateral Splanchnic Resection	4 hours, 41 minutes	4 minutes
				Bilateral Splanchnic Resection	3 hours, 30 minutes	1 hour, 15 minutes
R. M.	350531	Vagotonia	6 hours, 49 minutes	Atropine	5 hours, 12 minutes	1 hour, 37 minutes
				Vagotomy	2 hours, 50 minutes	4 hours
				Five months after vagotomy	2 hours	4 hours, 49 minutes



Fig. 1. Segment of a kymographic tracing showing the type of gastric motility observed prior to bilateral resection of the splanchnic nerves.

The results recorded on the kymographic tracings revealed some variation in the duration of periods of motility and in the amplitude of the contractions. Since it has been shown that the vagus nerve contains both motor and inhibitory fibers (21, 22), the results observed depend upon the existing tonus at the time of the experimental observations. McSwiney and Wadge (23) found that in a condition of low tonus, stimulation of the vagus with low or high frequency caused contractions and increased the tone. In a condition of high tonus, stimulation caused inhibition and relaxation. It has also been demonstrated (15) that stimulation of the peripheral cut end of the vagus by means of faradic current will if the organ be in a state of hypotonus either initiate movements in the quiescent stomach, or if movements are present, augment and sometimes accelerate them. The pre-existing state of the peripheral mechanism governs the response to stimulation, the most marked result being obtained with the active organ, the least with the passive.

The effect of vagus stimulation as reported in the literature has been variable. Van Braam Houckgeest (24) reported that stimulation of the cervical vagus caused contraction of the stomach. Bechterew and Mislawski (25) reported inhibition and associated the response with the strength of the stimulus. Bercovitz (26) and Rogers and Bercovitz (27, 28) obtained preliminary contraction followed by relaxation. Laughton (29) demonstrated in cats that stimulation of the dorsal vagus nucleus usually caused contractions, but inhibition also occurred if the tonus was high. Many variations are probably due to the fact that the effects of stimulation are governed by the existing gastric tonus at the time of stimulation.

During the administration of atropine, we observed a slight decrease in the duration of periods of gastric

motility. This was associated with a corresponding increase in the duration of periods of quiescence. The interval between contractions was somewhat increased and the number of contractions, many of which were of low amplitude, was also diminished. Associated with this general reduction in gastric activity, there was considerable symptomatic improvement.

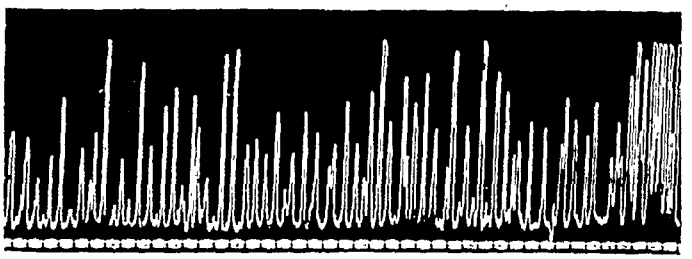


Fig. 2. Kymographic tracing showing intense gastric motility subsequent to bilateral resection of the splanchnic nerves.

Smith (30) and Brown and McSwiney (31), studying the effect of various drugs on gastric motility found that pilocarpine caused contractions of all parts of the stomach which were inhibited by atropine. McCrea and McDonald (32) and Carlson, Boyd and Pearcy (13, 14) also reported that atropine paralyzed the gastric musculature eliminating both vagus and splanchnic control.

There is convincing evidence to show that the left vagus exerts a greater influence on the gastric motility than the right. This was demonstrated by Batelli (33) and also confirmed by May (22). Laughton (29) has shown that faradic stimulation of the cephalic half of the left dorsal vagus nucleus resulted in a more marked effect on the stomach than stimulation of the corresponding part of the right dorsal vagus nucleus. Although McCrea and his associates (34) and McSwiney (18) reported that unilateral vagotomy was without effect, we observed striking changes following anterior (left) abdominal vagotomy. The outstanding feature of our observations was a definite decrease in the duration of periods of gastric motility (Figure 5), associated with a corresponding increase in the duration of periods of quiescence. The number and amplitude of the contractions were markedly decreased.

There was a marked increase in the interval between contractions. In many instances this ranged between nine and twelve minutes in contrast to an approximate average of two minutes during the preoperative control period.

This patient returned to the hospital about five months after left abdominal vagotomy for the investigation of the late results. At this time there was essentially no change in the gastric motility. The decrease in the duration of periods of motility still persisted (Figure 6). Periods of quiescence still remained increased, and the contractions were low grade and many of them feeble.

Our observations indicated that in the untreated vagotonic stomach, there was an abnormal retention of gastric contents. Four determinations on the emptying time made during the preoperative period revealed a variation ranging from five hours and thirty minutes to eight hours and averaged six hours and forty-nine minutes (Table II). It would seem at this time that the probable cause for this abnormal gastric retention was pylorospasm obstructing the outlet of the stomach.

During atropine medication three observations were made. The emptying time ranged from four hours and forty minutes to five hours and forty minutes, and averaged five hours and twelve minutes. Under the influence of this medication the pylorus appeared to be less spastic.

Following anterior vagotomy there was a definite decrease in the emptying time of the stomach. Three observations were made. The emptying time ranged

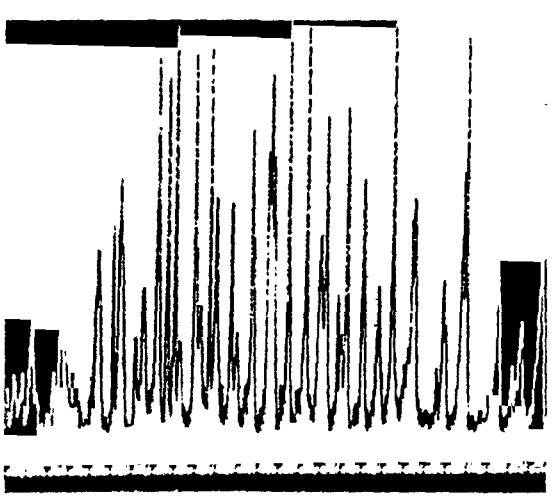


Fig. 3. Kymographic tracing seven months after bilateral resection of the splanchnic nerves. The amplitude of the contractions frequently measured from 11 to 14 cm.

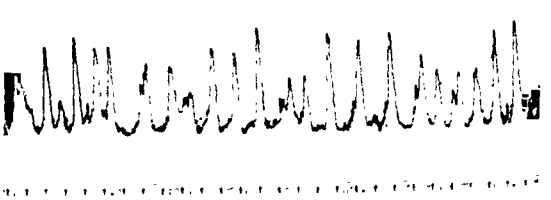


Fig. 4. Kymographic tracing showing persistent gastric motility in a patient with vagotonia. Frequently contractions of this type were observed throughout an observation period of three hours.

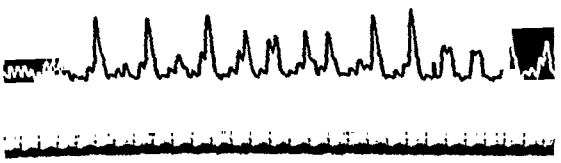


Fig. 5. Kymographic tracing showing gastric motility following vagotomy. There was a definite decrease in the duration of periods of activity and in the amplitude of the contractions.

from two hours and thirty minutes to three hours and fifteen minutes, and averaged two hours and fifty minutes, approximately four hours sooner than during the control period. Five months after vagotomy the emptying time was two hours.

It may at first seem paradoxical that a hypomotile stomach should evacuate its contents sooner than during the hypermotile control period. Our observations indicated that the decrease in the emptying time which ensued subsequent to vagotomy was due to the gravitation of barium through a patulous pylorus. In contrast to this, the increased emptying noted after bilateral resection of the splanchnic nerves was probably the result of increased gastric activity.

McCrea, McSwiney and Stopford (34) have pointed out that the immediate effects of vagotomy were unreliable and probably due to shock. Shortly after unilateral vagus section they observed a temporary paresis and dilatation of the stomach. After bilateral vagotomy there was a marked decrease in the initial emptying time as well as a decrease in the total emptying time which they attributed to a semi-patulous condition of the pylorus. Hughson (35) also observed a decrease in the emptying time. Laterjet, Cluzet and Wertheimer (36) however reported dilatation and atony of the stomach associated with a marked delay in the emptying time.

THE INFLUENCE OF THE EXTRINSIC INNERVATION ON CERTAIN GASTRIC ABNORMALITIES

Numerous investigators have reported various disturbances in the motor physiology of the stomach, subsequent to gastric denervation. Exner and Schwarzman (37) noted pylorospasm and cardiospasm. McCrea, McSwiney and Stopford (34) reported that this was temporary, probably due to irritation of the nerves. It has also been stated (36) that resection of the vagus nerves has prolonged gastric emptying. These findings could not be confirmed by Hughson (35) and Barron and Curtis (6).

The influence of the gastro-duodenal nerve supply in the production of gastric ulcer is still controversial. Lichtenbelt (38) sectioned the vagi under the diaphragm and found that gastric ulcer developed in 70 per cent of his dogs. This work could not be confirmed by Donati (39). Auer (40) also found ulcers in a number of his vagotomized rabbits. Duranti (41) also favored the neurogenic etiology in the production of ulcers. Beazell and Ivy (42) reported an incidence of ulcer in 41.6 per cent of their vagotomized rabbits fed a stock diet, but no evidence of ulcer in vagotomized rabbits which were on a diet of okra. They were unable to find gastric or duodenal ulcers in vagotomized dogs.

We were unable to ascertain any clinical, roentgenographic, or experimental evidence of gastric or duodenal ulcer in our patient subsequent to vagotomy. Numerous observations made until five months after vagus neurotomy revealed an uncomplicated clinical course. Symptomatic improvement continued and there was a sustained conspicuous gain in weight.

Gastro-duodenal denervation has been proposed for the surgical treatment of various gastropathies. From an anatomical study of the splanchnic nerves, Jean (8) recommended supradiaphragmatic resection of the splanchnic nerves in the management of gastric crises of tabes. Pieri (43) also advised this procedure for essentially the same conditions. Gianolla (44) and Pieri (45) performed vagotomy in the management of various gastric disorders and also for gastric ulcer. Encouraging results were noted. Klein (46) reported a series of eight cases upon whom left vagus resection in addition to partial gastrectomy was performed for duodenal ulcer with marked hyperacidity. During the postoperative period he observed anacidity associated with symptomatic improvement. Schiassi (47) also stressed the importance of the nervous element in the etiology of duodenal ulcer.

Contrary to the findings of these investigators, Steinthal (48) performed gastric denervation for gastric ulcer and on the whole formed an unfavorable opinion regarding this operation. Borchers (49) also decided against operations on the vagus nerves. Best and Orator (50) concluded from their investigations that section of the vagus nerves for the treatment of peptic ulcer was of little value.

The lack of uniformity in the results reported in the literature is certainly disconcerting. The failure to establish confirmatory evidence in favor of gastro-duodenal denervation for peptic ulcer no doubt accounts for its cool reception in the minds of many investigators. A critical analysis of many enthusiastic reports leaves us with a multitude of queries. Much of the buoyancy is not substantiated by basic physiological data so that in many instances there is no objective confirmation for certain empirical conclusions. Frequently the duration of investigation before and after operation was too short to evaluate accurately the merits of gastro-duodenal denervation.

Our own observations on the effect of bilateral resection of the splanchnic nerves and of vagotomy revealed no subsequent deleterious clinical complications. We cannot substantiate any views which maintain that pathological dilatation of the stomach ensues after vagotomy. We observed no clinical or roentgen-

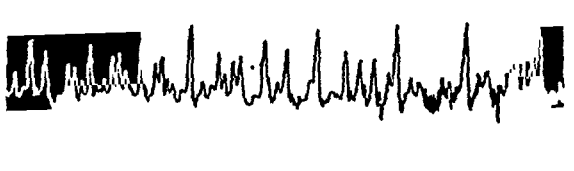


Fig. 6. Kymographic tracing five months after vagotomy. The decrease in gastric activity was still evident.

ological evidence of ulcer. Since so much confusion is already present regarding the role of the extrinsic innervation in the etiology and treatment of peptic ulcer, the present investigation, which deals with the basic physiology of the nervous control of the human gastric motor mechanism, was undertaken with the hope that it might cast some light upon problems which are still obscure.

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DISCUSSION

DR. HARRY SHAY (Philadelphia, Pa.): Dr. Barron's data point out certain things that to us are extremely interesting in so far as his findings may be interpreted as showing quite definitely that peristalsis, is not the important factor in gastric emptying. He calls peristalsis what we would rather call motility. We could confine the term peristalsis to the waves of contraction of the stomach, and motility to the actual emptying process. In spite of the increased peristalsis after bilateral splanchnic section, motility was not materially increased, yet, after vagotomy, and a marked decrease in peristalsis, Dr. Barron saw no marked decrease in motility. These findings would fortify the opinion we have often expressed from our own studies that peristalsis per se is not the important factor in gastric emptying.

DR. FRANKLIN W. WHITE (Boston, Mass.): I should like to ask whether atropine in active doses caused less gastric motility, and what doses were used?

DR. LOUIS E. BARRON (New Haven, Conn.) (closing the discussion): I should like to amplify a statement that was made by Dr. Shay. It was our experience that the increased emptying observed subsequent to bilateral resection of the splanchnic nerves was due to the demonstrated increased gastric activity.

The increased gastric emptying observed following anterior or left abdominal vagotomy was due to the gravitation of gastric contents through a patulous or semipatulous pylorus.

In answer to the second question, gastric motility was studied by the balloon and kymograph method. We were observing essentially the contractility of an empty stomach.

The dosage of atropine which we used was 75 minims a day. This patient had been in the hospital about a year prior to our investigation, and apparently had built up a tolerance to atropine so that no symptomatic relief was obtained with smaller doses.

The Effect of Osmotic Changes in the Small Intestine Upon Gastric Emptying in Man*

By

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and

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PHILADELPHIA, PENNSYLVANIA

IN previous reports we (1, 2, 5) have shown that the local mechanism controlling gastric motility and pyloric function is activated from the upper small intestine. This has since been confirmed in the experiments of Johnston and Ravdin (3) and of Cerqua (4). We have also demonstrated that the intrinsic agent which stimulates this mechanism is the gastric hydrochloric acid after it has passed the pylorus. Other agents which may be ingested and which may be equally efficacious in modifying gastric and pyloric functions have also been studied. Of these, the effect of fat, milk and cream has already been reported (5). Our present report is concerned with the influence of duodenal osmotic changes upon that same mechanism. The experimental method used was identical with that described in previous publications (1). Briefly, it consisted of frequent roentgenologic observations and roentgenographic records of the gastric emptying of a standard water-barium meal, taken by mouth, while the duodenal stimulant at body temperature was instilled through a duodenal tube. We studied the influence of the various stimulants administered by mouth by adding them to the standard water-barium meal, the volume of the ingested meal being constant. The standardization of the patient and the precautions taken in the study were exactly as those described in previous reports.

Twenty-seven subjects were used for the present investigation. Of these, four had achlorhydria; three, hyperchlorhydria; and twelve had shown a normal gastric acid response to the fractional Ewald Test. The remaining eight patients had had previous gastric operations. Of these, six had had a posterior gastroenterostomy and two had been subjected to a partial gastric resection of the Polya type. All the subjects were apparently in good health during the period of investigation. A total of 221 motor studies was done in this group of experiments. The data obtained with similar test agents were strikingly uniform. A few protocols which show the average findings probably offer the best means of examining our results. We have selected for illustration the data obtained in a patient with achlorhydria.

THE EFFECT OF THE TEST AGENTS ADMINISTERED ORALLY

B. S. evacuated the standard water and barium mouth meal leaving a 10% gastric residue after thirty minutes (Fig. 1). Three times this same result occurred within the limits previously described (1). A normal saline meal was evacuated in like manner in the same interval. A barium—5% glucose meal left a 15% gastric residue at the end of thirty minutes, a response like that obtained with tap water or normal saline. A greater concentration of glucose, however, resulted in definite changes in gastric motility. Thus a 20% glucose meal was emptied more slowly and left a 50% gastric residue at the thirty minute period. A

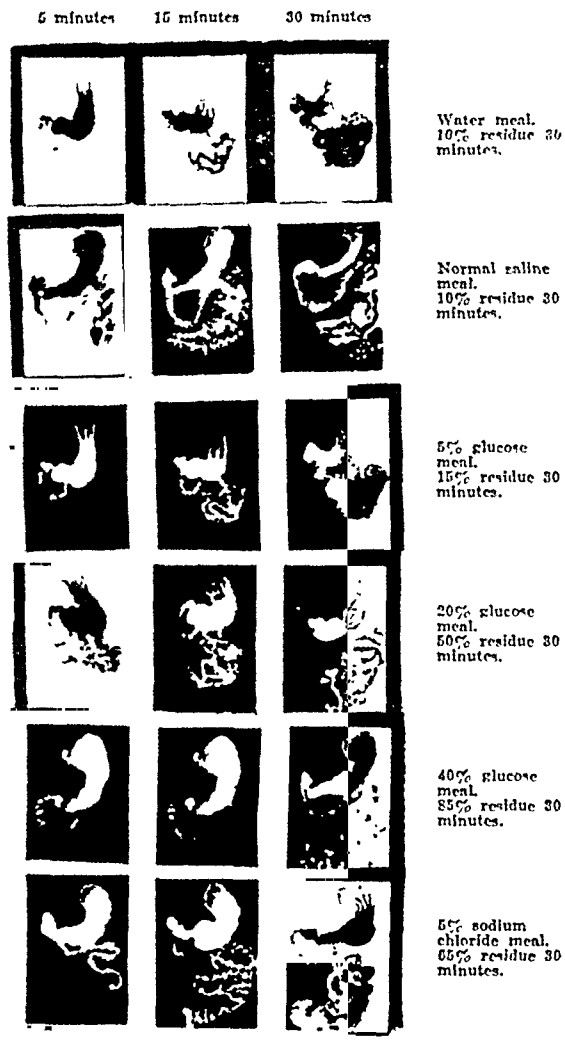


Fig. 1. Evacuation of iso-and hypertonic meals. (Pen and ink drawings of roentgenograms).

*From the Samuel S. Fels Research Fund and the Gastro-Intestinal Division, Medical Service I, Mt. Sinai Hospital, Philadelphia, Pa. Presented at the Annual Meeting of the American Gastro-enterological Association, Atlantic City, June 7th and 8th, 1937.

very striking retention was found in the stomach at the same time interval when a 40% glucose meal was administered. In this instance, 85% of the gastric contents had not yet passed the pylorus at the end of half an hour. A similar marked delay in gastric emptying was obtained with a hypertonic sodium chloride (5%) mixture. Following such a meal, 65% was still present in the stomach at the time interval although the normal saline meal had been practically emptied.

EFFECT OF THE TEST AGENT INSTILLED DIRECTLY INTO THE DUODENUM

Even more striking were the differences in gastric motility from the direct duodenal instillation of agents isotonic and non-isotonic. The intensity of these changes, within certain limits, was proportional to the degree of variation from isotonicity of the test agent used.

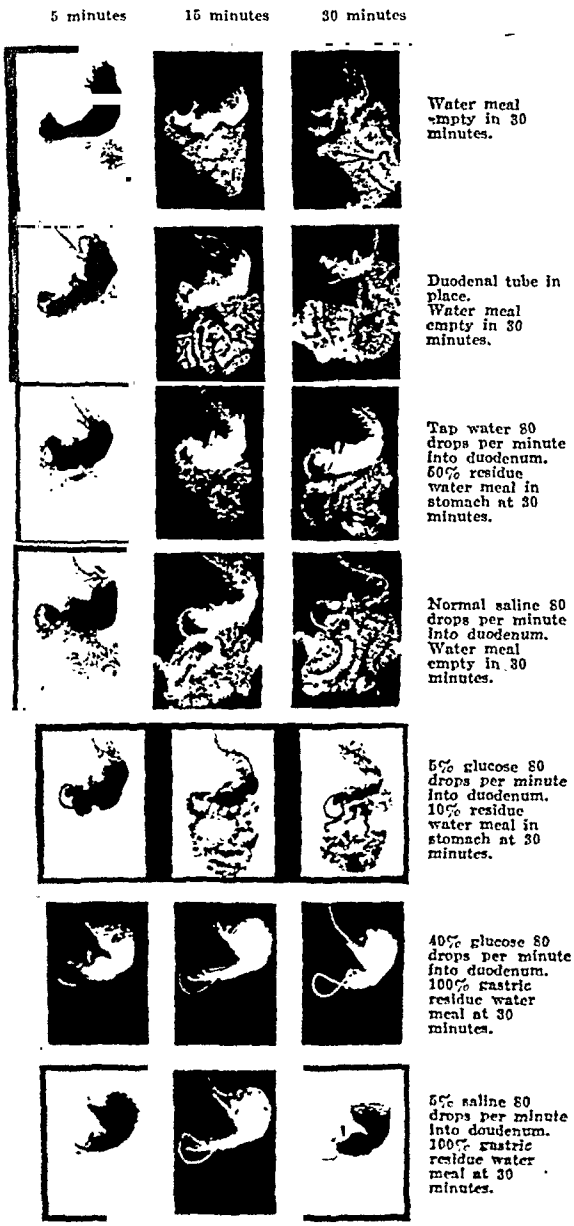


Fig. 2. Effect of osmotic tensions in duodenum on gastric evacuation.

In this group as well as in those previously reported, a possible influence of the presence of the duodenal tube through the pylorus upon gastric motility was sought. Again no change in gastric motility, as a result of the tube alone, was found. It is extremely interesting to contrast the results obtained (Fig. 2) after the duodenal instillations of water and of normal saline. It should be noted that the presence of normal saline in the duodenum did not retard the gastric emptying of the water and barium mouth meal in the slightest. Following the duodenal instillation of tap water there was a marked delay in the evacuation of the barium-water mouth meal (50% gastric residue)—a striking contrast to the 10% gastric residue at the end of 30 minutes when the water and barium meal had been taken by mouth (Fig. 1). These differences, we feel, are adequately explained on the basis of a rapid adjustment of gastric osmotic conditions toward isotonicity and they also stress the extreme sensitivity of the duodenal mucosa to conditions away from isotonicity. Thus Ravdin, Johnston and Morrison (6) studying the concentrations of glucose in the stomach and intestines of the normal dog after intragastric administration, found that the introduction of hypertonic solutions into the stomach was followed by a rapid increase of the volume of the gastric contents and a decrease in their concentration. Our own studies (7) in man resulted in similar changes, there being always an attempt to bring the ingested fluid to the isotonic state. In the same way, ingested tap water tends rapidly toward an isotonic solution because of the salt content of the gastric juice. We see, therefore, very little, if any, difference between the gastric emptying of tap water and of normal saline, when taken by mouth. When, however, the tap water is instilled directly into the duodenum, the sensitive duodenal mechanism is stimulated by the hypotonic tap water thus effecting a change in the pyloric mechanism and in gastric motor emptying.

Again the intraduodenal instillation of 5% glucose (Fig. 2) caused no appreciable change in the emptying of the water and barium mouth meal. When, however, a 40% solution of glucose was substituted for the 5% agent, practically complete pyloric closure was obtained and resulted in a 100% gastric retention of the mouth meal during the usual period of observation. A hypertonic (5%) solution of sodium chloride produced a result identical with that seen following the use of the 40% glucose solution (Fig. 2).

Alkalies, when taken by mouth or instilled directly into the duodenum, produced changes in gastric motility in the achlorhydric subject, which depended entirely upon the osmotic effect of the solution used (Fig. 5 and 6). Thus, a 1% solution of Sodium Bicarbonate (essentially isotonic) had no influence over gastric emptying while a 5% solution had a very marked effect. In the patients with gastric acid secretion, these effects were, of course, modified by neutralization of the bicarbonate through contact with the gastric acid (Fig. 5 and 6). Thus, we see an increased gastric emptying in the normal acid patient following the 1% sodium bicarbonate mouth meal as compared with the water and barium meal alone. This

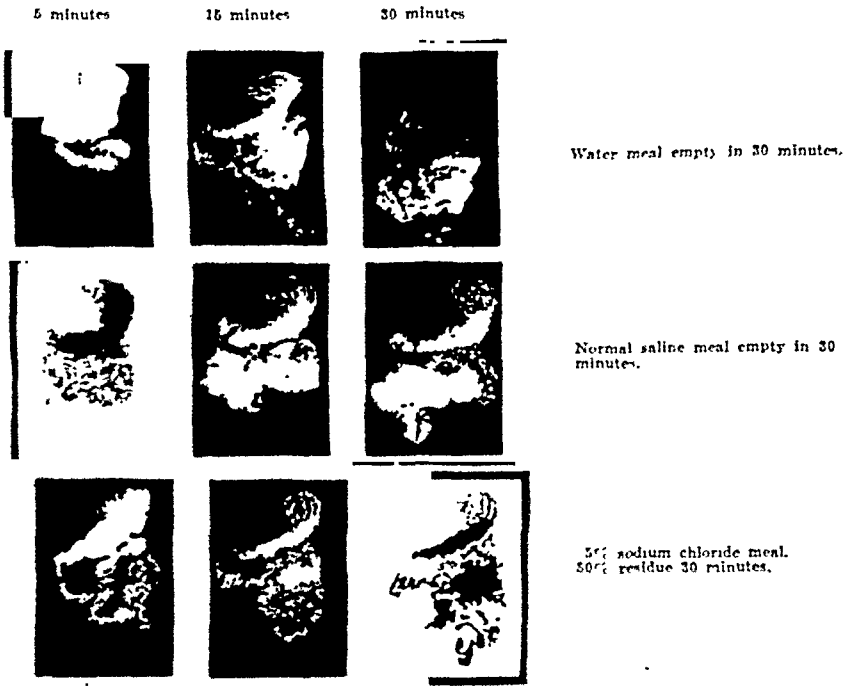


Fig. 3. Effect of osmotic pressure changes in stomach with posterior gastro-enterostomy.

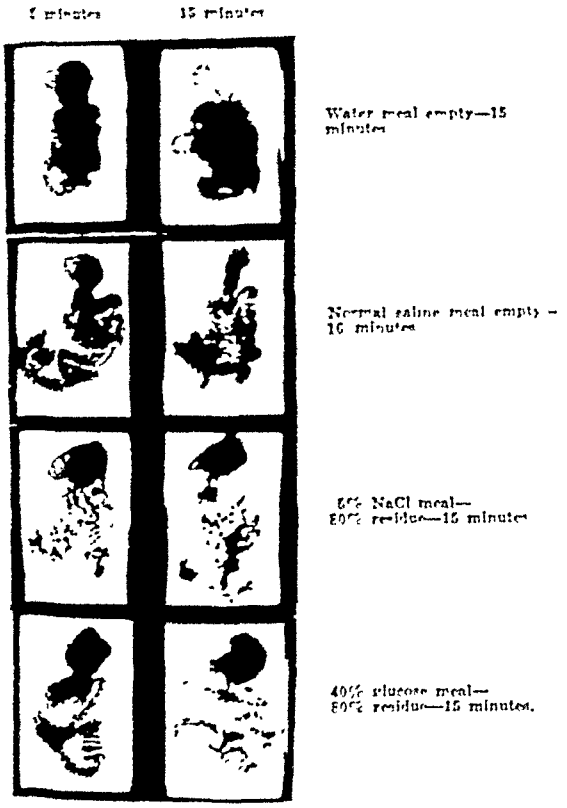
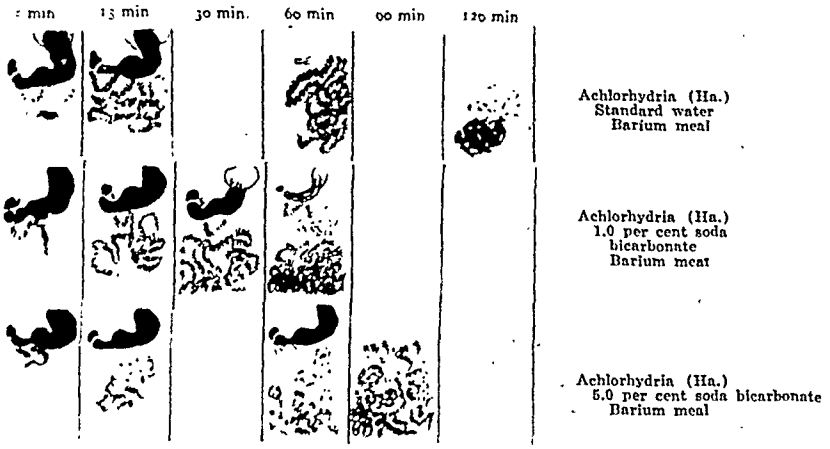


Fig. 4. Effect of osmotic pressure changes in stomach after polya operation.

is also true after the duodenal instillation of the 1% bicarbonate. The 5% bicarbonate solution, however, adds physical factors not offset by the acid neutralization, so that a marked effect on motility is seen even in the normal acid patient. This is especially true when the bicarbonate is instilled directly into the duodenum. Keeping in mind that the osmotic effect of the alkali will be altered by the rapidity of neutralization by the acid in the normal and hyperacid patient, any variations in motor effects will be readily explicable.

The behavior of the operated stomach, whether resected (Fig. 4 and 7) or following gastro-enterostomy (Fig. 3), was similar to that of the intact stomach, except for quantitative differences. The resected stomach, as previously reported (2) for acids, alkalies, and fats, responded to changes in osmotic conditions in the intestines identically as the intact stomach, except that a similar stimulus produced a less marked effect in the operated patient than it did in the non-operated. The behavior of the gastro-enterostomized stomach was similar to that of the resected type. Ravdin, Pendergrass, Johnston and Hodes (8) have observed roentgoenographically the slow gastric evacuation of hypertonic solutions in both dog and man with intact gastro-intestinal tracts, as well as after gastric operations. Probably the earliest detailed studies of the role of osmotic pressure upon gastric emptying were those of Carnot and Chassevant (9, 10) in 1905. In duodenal fistula dogs they found that isotonic solutions of saline or glucose produced a series of pyloric openings which permitted the solutions to course very rapidly by successive jets from the stomach into the intestines without undergoing great modification. If, however, the solutions were appreciably far from isotonicity, the contact of the first portion of the liquid with the duodenum provoked



Response of *achlorhydric* stomach to test substances using mouth meal.

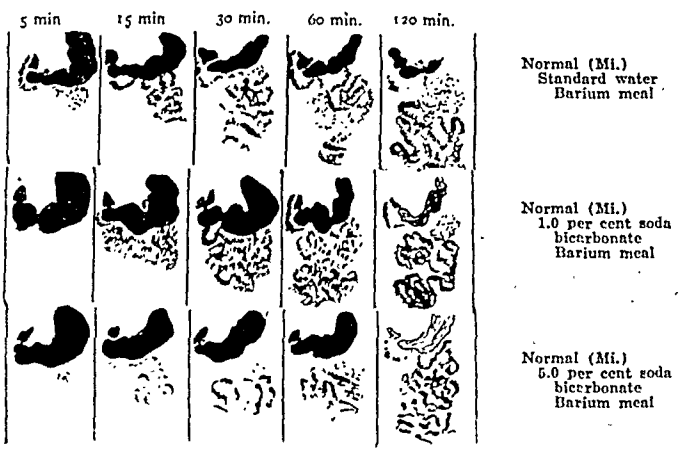


Fig 5

Response of *normal* stomach to test substances using mouth meal.

reflex closure of the pylorus, which did not reopen until proper dilution of this portion had taken place.

More recently McSwiney and Spurrell (11) very carefully studied the influence of osmotic pressure on the emptying time of the stomach. They made very searching calculations of the relationship between the degree of osmotic pressure change and the delayed gastric emptying and concluded that relatively small changes in the former caused very marked delay in the latter. Johnston and Ravdin (3) have stressed the influence of varying concentrations of glucose on the emptying of the normal and operated stomach.

The rapidity with which pyloric closure and cessation of gastric evacuation follow the duodenal instillation of hypertonic or hypotonic solutions, makes the reflex closure suggested by Carnot and Chassevant (10) and later by Wheelon and Thomas (12), a likely explanation for the mechanism involved. Yet the results obtained by Quigley, Zettleman and Ivy (13) in dogs with completely denervated entire stomach pouch preparations, and by Quigley and Phelps (14) with auto-transplanted denervated pouches make a consideration of a humoral factor in the dog at least essential to the understanding of the duodenal mechanism in gastric motor control.

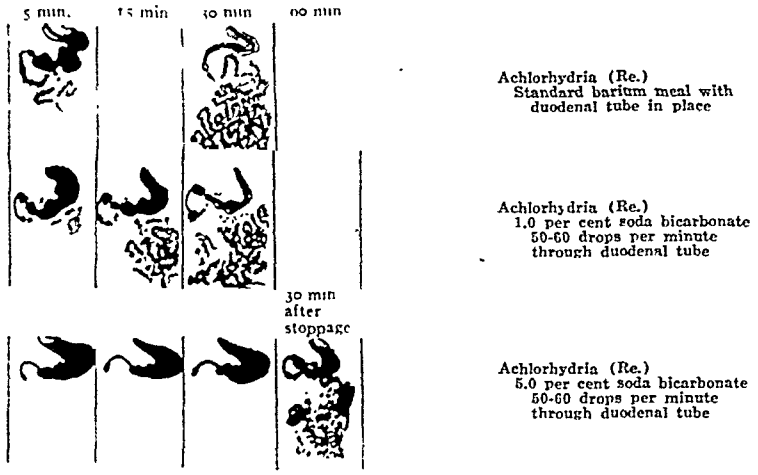
CONCLUSION

For the same reasons that we concluded the pyloric action was motivated locally through duodenal stimulation by chemical action, we conclude that this same mechanism is influenced by physical stimuli as represented by changes in osmotic pressure away from isotonicity. Gastric emptying time alone cannot be used as an index of pyloric function when considering osmotic tension of agents given by mouth because of the migration of fluid which takes place through the stomach wall when the test meals are not isotonic.

We should again like to draw attention to the necessity of considering the type of test meal when measuring gastric motility. Roentgoenologists, especially, must realize that no comparison of gastric motor data can be possible, if the test meals vary either in chemical or physical composition.

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Response of *achlorhydric* stomach to test substances during duodenal instillation.

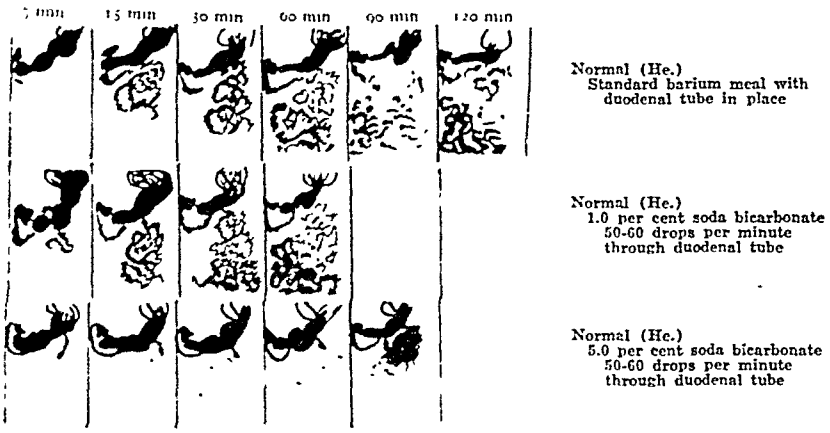


Fig. 6.

Response of *normal* stomach to test substances during duodenal instillation.

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DISCUSSION

DR. HARRY SHAY (Philadelphia, Pa.): The first question regarding the position of the tube in different portions of the intestinal tract—we have studied the effect of intestinal instillation of various agents into the duodenum, upper and lower, and into the jejunum as well. The further you get away from the pylorus, the less marked is the effect of similar stimuli.

We are in accord with the concepts of Dr. Thomas and Dr. Quigley, but I am afraid we can't agree to disregard the rôle of the hydrochloric acid in the mechanism concerned. We believe that the hydrochloric acid is the normal intrinsic agent that activates this mechanism, but that other agents added by foods may be equally efficacious. This brings us to some of the points raised by Dr. Eusterman and will explain some of the things that he discussed. We have in previous publications reported the effects of acids and alkalis by mouth and by duodenal instillation. We have there shown that we could radically change the motor function of an anacid stomach by changing the ingested meal from tap water to only .09% hydrochloric acid. I think in this lies the answer to the good clinical results seen from the administration of what chemically are certainly inadequate doses of hydrochloric acid. The good result being an effect on the gastric emptying and a changed intestinal picture. We feel that

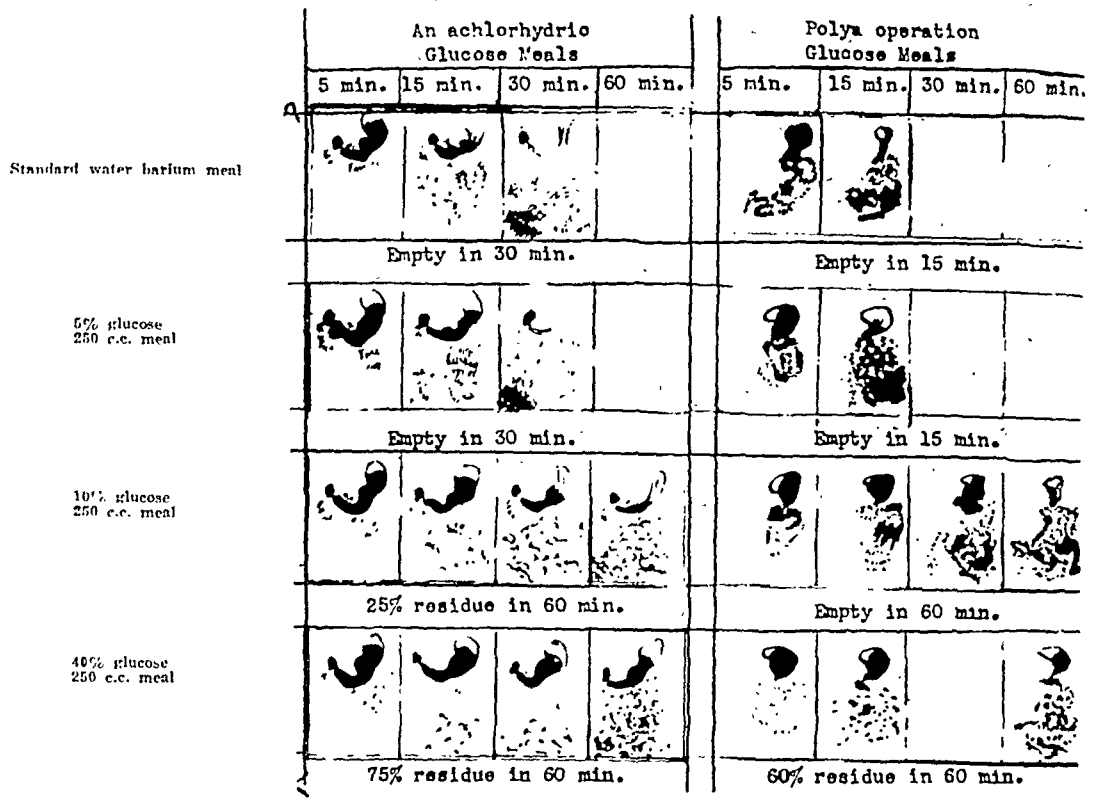


Fig. 7

gastrogenous diarrhea may in many instances be an expression of the rapid gastric emptying.

Regarding the cryoscopic index in the discussion of Dr. Rehfuss, we believe that this again is an expression essentially of the thing we talked about today; namely, the changes in osmotic pressure. We are, in the main, in agreement with the discussion of Dr. Necheles, but he, too, favors disregarding the hydrochloric acid as a factor in the mechanism. To this departure, certainly from a clinical standpoint as well as from our own experiments in the human subject, we cannot subscribe.

DR. J. PAUL QUIGLEY (Cleveland, Ohio): We have been carrying out some experiments which have a direct bearing on the material presented by Dr. Shay. Working with dogs, we have employed the balloon method; individual balloons inserted in the pyloric antrum, pyloric sphincter, and the duodenum by the method of Dr. Thomas which I think is familiar to all of you. With this technic, we have found that hypotonic solutions (represented by distilled water), or hypertonic solutions (represented by 2 per cent sodium chloride solutions), when introduced in the *stomach* had no effect on the three regions mentioned.

When these solutions were introduced in the *duodenum*, they did modify motility, but they always depressed the motility of the stomach, the sphincter and the duodenum. This depression was never very marked, so in comparison with fats and other substances we have investigated, I feel that *modifications in isotonicity are not very important.*

Dr. Thomas' statement that food products actively influence the pylorus and adjacent structures is quite in line with our findings. We are also in agreement with his observation that hydrochloric acid is of less importance. We have introduced at frequent intervals small quantities of hydrochloric acid into the duodenum while recording motility from the pyloric antrum, sphincter, and duodenal bulb. When quantities of 2 c.c. of 0.2% acid were employed practically no significant change occurred in the motility of these structures. If we used larger quantities or higher concentrations (beyond the limits which we consider physiological) we obtained inhibition.

I do not feel that hydrochloric acid is important in controlling the sphincter, antrum or bulb. So far as such studies as we have made can be employed for the interpretation of gastric evacuation mechanisms, hydrochloric acid or moderate variations in osmotic tension of solutions is probably not particularly important in regulating the gastric emptying process.

DR. GEORGE B. EUSTERMAN (Rochester, Minnesota): Several authorities have recently challenged the statement that the achlorhydric stomach does not empty any faster than the one with normal acid content. It has been our experience that the former does empty more rapidly in the majority of cases, granting there is no marked disturbance in the tonicity of the organ and no mechanical obstruction. Some years ago Wheelon, by physiologic studies on the experimental animal, showed that nausea and vomiting are the result of duodenal antiperistalsis. By increasing the pH of the duodenal content he was able to prevent, or reduce, this reversal of peristalsis, with subsidence of nausea and vomiting. He largely achieved this by the addition of hydrochloric acid or sodium chloride. Under certain conditions I have found this chloride or acid therapy to be effectual, and I would like to ask the essayist whether his observations in this field have any bearing on the management of some of our ordinary daily clinical problems.

DR. HEINRICH NECHELES (Chicago, Ill.): We are conducting some experiments just now on the emptying

time of the stomachs of dogs, which I think confirm and complete the observations of Dr. Shay and Dr. Thomas, and Dr. Quigley. We were not satisfied with the small doses of hydrochloric acid that are given (ten to twenty drops of 0.5 per cent solution). We acidified the barium-meal, so that we brought it down to a pH of two to three, or we alkalinized it and we found in a great number of experiments on dogs that this had practically no influence on the emptying time.

On the other hand, I want to remind you of some older work by Kestner and Never, who showed that rather dilute concentrations of hydrochloric acid produce contractions of the intestine. They demonstrated this in a very simple experiment. They took the small intestine of a guinea-pig and perfused its lumen with a very dilute solution of hydrochloric acid—I think it was between N/30 and N/50. There was a marked delay in the passage of this solution as compared to Ringer's solution.

DR. RALPH C. BROWN (Chicago, Ill.): I should like to ask if it made any difference what position the tube was in, whether the tip of the tube was in the first or third portion of the duodenum and as to whether any observations were made on this point.

DR. J. EARL THOMAS (Philadelphia, Pa.): These observations and previous observations of Dr. Shay along the same line are of great interest to the physiologist. They emphasize something which is becoming very important, namely, that substances other than hydrochloric acid can influence the emptying time of the stomach.

The knowledge of such substances is increasing rapidly. We can include fat, which has been known for a long time; carbohydrate, and as shown this morning, hypertonic and hypotonic solutions. Recently it has been observed that the products of protein digestion when placed in the intestine inhibit gastric motility; thus we have included all the three types of food among the materials which, when present in the intestine, may delay gastric emptying.

Why are we interested in substances other than hydrochloric acid? Evidence is accumulating that hydrochloric acid seldom reaches the intestines in quantities adequate to influence gastric motility. I believe it was Dr. Carlson who first remarked that free hydrochloric acid is hardly ever found in the duodenum. pH 3.6 represents the minimum acidity attained in the duodenum even with the foods that develop the greatest acidity. Some incompleted experiments of ours tend to show that the threshold acidity for inhibiting gastric emptying is around pH 2. Those of you familiar with that notation realize that between pH 2 and pH 3 there is a difference of about 1000 per cent, so that it is difficult to believe that in the normal stomach following an ordinary meal gastric emptying is regulated by hydrochloric acid in the intestine, as we have so long believed. It is very useful, therefore, to find these other substances which are capable of inhibiting gastric motility and thus of regulating the emptying of the stomach.

I think we can say now that the bulk of physiological evidence indicates that the products of digestion and the food substances themselves are the main factors in the regulation of gastric emptying by means of stimuli arising in the small intestine.

DR. J. EARL THOMAS (Philadelphia, Pa.): I want to ask whether the motility recorded was peristalsis after meals or merely hunger activity.

A Theory on the Formation of Peptic Ulcer*

By

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CHICAGO, ILLINOIS

THE newer knowledge that stimulation of parasympathetic nerves liberates acetylcholine, and the discovery by Dale and Feldberg (1) that stimulation of the gastric vagus results in the appearance of acetylcholine in the venous blood from the stomach has opened a new approach to the problem of the genesis of peptic ulcer. Although acetylcholine dilates peripheral blood vessels the effect of minute amounts of this substance on the circulation of the stomach had to be investigated. This was done by us on arteries, veins and capillaries isolated from fresh human stomachs as well as on rats' and dogs' stomachs (2-4). It was found that acetylcholine produces a diminution of flow through isolated vessels. In perfusion experiments on the rats' stomach acetylcholine practically always effected marked vaso-constriction while controls, namely the legs of the same rat, responded with vasodilation to the same quantities of acetylcholine. In order to test an animal whose stomach resembles more the human one, the dog was used. The stomach of one animal was viviperfused by another larger dog and blood flow through that stomach was measured. In another series of experiments the stomach of a dog was prepared so that the blood flow through the gastric vein could be measured. In a third series of dogs oncometry of the entire stomach was performed. The results showed that in the greater number of experiments small doses of acetylcholine comparable to those liberated when the vagi are stimulated, produce diminished blood flow through the stomach, the diminution amounting to from 60-96% in some of the experiments (4). We may conclude, therefore, that over-production and, more particularly, a continuous production of acetylcholine in the stomach will produce an anoxemia of its tissues. Such an anoxemia will be more severe in those regions in which most branches of the vagus nerves are distributed and will be more fateful in such parts where end arteries occur, namely, on the lesser curvature of the stomach and in the duodenal bulb.

Devitalized gastric and duodenal tissues are digested rapidly by the gastric and duodeno-pancreatic juices. We have found that these tissues are dissolved also by weak HCl and sodium bicarbonate solutions without the presence of enzymes (unpublished). In experiments on frogs we have seen that alternating exposure to active trypsin and pepsin solutions effects

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From the Michael Reese Hospital, Chicago, Ill.

much faster and much more thorough digestion than active pepsin alone (7).

In the light of the experiments and facts cited above, one might expect to obtain the greatest incidence of ulcers in the duodenal cap and next to it on the lesser curvature, where alternating exposure to active trypsin and pepsin takes place regularly, where at the same time end arteries occur and where most branches of the vagus nerves are found, i.e., where most acetylcholine is produced.

A fundamental question in the above theory is whether persons with peptic ulcer really produce more acetylcholine in their stomachs than normal persons. Many facts support this assumption. Acetylcholine is able to produce powerful contractions of the stomach and intestine as well as acid secretion of the stomach (4-6, and unpublished experiments). Gray, from Ivy's laboratory, reported in Memphis (16) that small amounts of acetylcholine raise gastric acid secretion and that larger amounts suppress it. In a number of tests on Heidenhain dogs we have been able to confirm Gray's findings against those of the Boston group (17). In addition to this, we have found that acid secretion produced by histamine is first stimulated and then decreased by acetylcholine.

Confirming Winkelstein we have shown that patients with duodenal ulcer have a higher appetite secretion than normal subjects (8, 9). This points to greater vagus effect in ulcer patients. A higher and more constant acid secretion after meals and during the interdigestive phase, that is, during the night points to the same fact. Hypermotility of the stomach, which we have found even in ulcer patients after sub-total gastric resection, and which we find is more or less common to all patients with duodenal ulcer may be due to a greater activity of the vagus or of Auerbach's plexus (10). We have not found a change in dermographic reaction time in ulcer patients as reported by others but we do find a jump in the dermographic reaction time around the age of 30 which may point to capillary changes at this age, at which period, coincidentally, ulcer begins to occur more frequently (11).

One fact, which we find difficult to class with the above consideration, is our finding that peptic ulcer patients secrete less saliva to pilocarpine stimulation than a comparable group of normal subjects (13). This is somewhat opposed to the findings of Winkelstein (14). It is probable, however, that in persons with peptic ulcer only certain centers in the mid-brain may be hyperactive and others not. It also may be that the overactivity in one center may depress other centers. The above observations favor the concept of "autonomic imbalance" in ulcer patients.

It may be unnecessary to add that most ulcer patients are persons of the worrying and high strung type. A fact that favors the assumption of a constitutional factor in peptic ulcer can be seen in our results on the gastric secretion in the normal relatives of ulcer patients (12). In 82 such healthy male and female relatives of ulcer patients not having any gastro-intestinal complaints, distinctly low values for free acid were found after an Ewald meal while the residue of the fasting stomach in the greater number of instances, contained a high degree of free acid. From these findings the question arises whether peptic ulcer begins as a gastritis and whether the hyperacidity of the duodenal ulcer develops later.

There is another question, namely, whether the decreased amount of visible mucus which we have found after pilocarpine stimulation in persons with duodenal ulcer (15) as well as the decreased amount of dissolved mucus which Fogelson reported in ulcer patients is due to an accompanying gastritis or to the effects of acetylcholine on the mucus glands of the stomach. This is under investigation.

With regard to ulcer therapy not much can be said at present except this: The only two agents known to counteract acetylcholine effectively are acetylcholine esterase and atropine. The concentration of acetylcholine esterase in the blood has not been found to be diminished significantly in peptic ulcer. It is a rather constant value and apparently changes only in wasting diseases. We have found one organ which secretes it in large amounts, namely, the pancreas, but pancreatectomized dogs did not show a diminished blood esterase and in acute experiments loss of pancreatic juice after secretin stimulation did not effect the esterase level of the blood (18). Yet if one could find means of raising the concentration of esterase in the blood it might be very much worth while to try this on persons with peptic ulcer.

Concerning the use of atropine in the therapy of peptic ulcer, it is apparent that if this drug is expected to relieve vasoconstriction possibly existing in the stomach of ulcer patients it must be given in such a way that it is effective for 24 hours of the day, a problem which does not seem to be unsurmountable.

CONCLUSION

I want to say that I have not put forward the above theory for the sake of itself, but because many experimental facts speak in its favor and because it may lead us further in the field of research and therapy. I gratefully acknowledge the help of my collaborators, whose names I have not been able to mention in this short account of our work.

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DISCUSSION

DR. EDWARD S. EMERY (Boston, Mass.): This theory which Dr. Necheles has put forward certainly deserves serious consideration because by it one can correlate many clinical and laboratory findings. It involves two problems, one the pharmacology of acetylcholine; the other, clinical observations. So far as the pharmacology is concerned, I do not feel capable of discussing it. I talked to some of the pharmacologists before coming down here and there seems to be some difference of opinion as to the normal concentration of acetylcholine in the body.

So far as the clinical side is concerned, I can agree with what the speaker has said concerning the increased secretion in patients with ulcer.

I should like to say just a word about the neurogenic theory. It seems to me that clinically we should be cautious as to how we interpret our findings. The neurogenic theory has received great impetus in recent years as a result of Harvey Cushing's statements, but nervousness is a complication of any chronic disease. When one talks with the asthma or the arthritic specialists, they speak also of nervousness as one of the important complications of the disease in which they are interested. We know that the gastric acidity plays a definite role in peptic ulcer, yet it is often difficult to evaluate the influence which the acidity exerts on the behavior of an ulcer in any one patient.

The same is true of nervousness. It is undoubtedly true that nervousness is a common cause of the recrudescence of symptoms in these patients, but we see a not inconsiderable number who are not unusually nervous. Therefore, with our present evidence, it is impossible to say that peptic ulcer is a neurogenic disease.

For the last few years we have tried, because of the work of Williamson and Mann and other experimentors, feeding ulcer patients with bile, without any success. More recently we have been trying feeding raw pancreas to these patients. To date the number of cases is very small, but so far we have not been able to demonstrate any value from this treatment.

DR. B. M. BERNSTEIN (Brooklyn, N. Y.): For the past two years Dr. Matzner and Dr. Windwer, in our department have been working on the production of experimental ulcer in the rat. My participation has been that of an observer and adviser. A number of important facts have been brought out which we are continuing to study and hope to present at a future time.

In the first place we produced ulcers in the rats by feeding and starving on alternate days. We found when we fed the rats hydrochloric acid in excess on the fasting days, we produced ulcer lesions in 10 per cent of the rats. When we gave pepsin, we found in the same way lesions in 85 to 90 per cent of a large number of rats. The problem arose as to whether we couldn't prevent the formation of these ulcers by in some way inhibiting the effect of pepsin.

We first thought we would use the ordinary food stuffs and this is most interesting, particularly in the light of Dr. Shay's paper. We found that when we fed these rats on the fasting days, fat or olive oil, and on other days carbohydrate as glucose solution, and other days on other group rats, protein, the following findings appeared: The rats that had fat with the pepsin and hydrochloric acid, developed ulcers in 70 per cent of the number used. Those with glucose developed ulcer in about 50 per cent; and those with protein developed them in a small percentage of cases.

How to evaluate these findings is rather difficult because we have several factors to deal with. Shall we say that the protein simply absorbed the pepsin, and in that way inhibited its action? That is one possibility. Hypoproteinemia can produce ulcers as has been shown by other workers.

Another theory comes to our minds this morning in the light of this paper and that is that fat and carbohydrate retard the emptying time of the stomach; protein apparently does not and, therefore, permits the pepsin to get in its effect over a longer period of time and produces ulcers more frequently and more routinely.

We haven't started yet on our clinical work. We hope to do so in the fall.

DR. GEORGE B. EUSTERMAN (Rochester, Minnesota): I feel that modesty should characterize any discussion of the pathogenesis of ulcer, for after all we may not know anything about the real fundamentals. The mechanism of its formation is somewhat more clear. What actually starts it and destines the acute lesion to become a chronic one still remains obscure. However, the Society is to be congratulated on having such competent workers and members as Doctors Necheles, Shay, Ivy, Mann and others, present the results of their investigators for our elucidation and consideration.

In discussing the problem of etiology with one of my associates, Doctor Mann, who has done such fruitful work in this field, one soon realizes that he is not a proponent of the vascular theory of ulcer genesis, which I think originated with Virchow. In Mann's extensive experimentation on animals he never was able to produce a chronic ulcer by interfering with the arterial supply to portions of the gastric mucous membrane, even though such interference was often very extensive. On the contrary, he maintains, and his results plainly show, that such lesions begin on the mucosal side, the result chiefly of chemical and mechanical factors. No work has been so outstanding or so generally accepted as that of Mann and Williamson in this respect, and other investigations by his colleagues of a similar nature.

One other successful way of producing the chronic lesion experimentally is by the injection of toxic doses of cinchophen. But such procedure is more or less out of line with human experience, and surely the latter is a constant reminder of the overwhelming importance of the acid or chemical factor in ulcer genesis, irrespective of how it may be brought about. This combination of maximum concentration, spasm, hypersecretion and concomitant retention of secretions through spasm, is the great mischief maker in the majority of cases, to my way of thinking. In this connection proponents of the psychogenic theory, that is, the effect of certain emotions on visceral function mediated by the sympathetic nervous system, have an increasingly strong argument. But the experimental physiologist, like Mann, will strongly disagree with you as regards the importance of the vascular role in ulcer genesis.

DR. HEINRICH NECHELES (Chicago, Ill.): As to the question asked by Dr. Emery about concentration of acetylcholine in the body, there is probably no acetylcholine whatsoever in the circulating blood except when the esterase is inhibited, which probably does not occur under physiological conditions.

Apparently the main point in this question is whether at the focus of production the acetylcholine is active or not, and I am convinced that it is, that the blood cannot destroy it as fast as it is produced at the endings of the vagus nerves. If we inject acetylcholine intra-arterially, we obtain violent contractions, in fact, the most violent contractions of stomach and intestines. If we give it intravenously, there are hardly any contractions, hardly any effect, except when we give it continuously and in huge doses, because it is destroyed so quickly.

As to the question of sympathicotonus, I think that we may favor the concept of autonomic imbalance; that is to say, a prevailing effect of the vagus center, either in the way of lack of inhibition or of overactivity, and I think that this view is sustained by a number of experiments which I cannot mention now.

Gastric acidity in ulcer, as I tried to explain, probably plays a small role, because, first of all, we know that ulcers may heal while gastric acidity is very high, or that ulcers may develop in patients with a very low gastric acidity. Very little acid and very little pepsin are needed for digestion of a devitalized spot in stomach or duodenum.

To Dr. Bernstein's argument, I agree, except that the rat has a pro-stomach and a stomach, and that it is difficult to draw conclusions from most animals except the dog and monkey, because the stomachs are so different. I was well aware of this difficulty in the question of hyperacidity of duodenal ulcer and the normal or subnormal acidity of gastric ulcer which Dr. Winkelstein mentioned. I did not want to go into it because it would take too much time. I just want to mention the possible effects of an accompanying gastritis as well as reflexes from the duodenum or from the lesser curvature which may explain such differences. I am not convinced yet, however, that duodenal and gastric ulcer are produced exactly by the same causes, although my experiments tend to indicate this.

Dr. Eusterman mentioned experiments which have been done long ago. I know the literature on ligation of arteries to the stomach of the dog. I think when we deal with end arteries, ligation of the big branches which we can get on the lesser and major curvature will not teach us very much because there are sufficient collaterals before the end arteries. Besides, I do not know of any work that shows that vascular-anatomic conditions in the dog's and in the human stomach are the same. Maybe Dr. Eusterman can answer that.

Dr. Rehfuss's work has interested me very much. I didn't know some of the facts, and I will be very much interested to consider all this.

In conclusion, I should like to mention one more fact which I forgot to bring out. The group of workers in Boston have shown that injection of mecholyl inhibits gastric acidity. A worker from Ivy's laboratory has reported that small doses given continually produce high acid secretion of the stomach and larger doses inhibit secretion. We have been able to confirm this latter result in a great number of experiments, and we have found that histamine increased the volume of this secretion, and then depressed it, a fact which may be of some importance in the physiology of secretion.

Again in conclusion, I want to stress that I have not put out this theory as a proven thing but rather as a guide to further research on the physiology and on the pharmacology of duodenal ulcer.

DR. ASHER WINKELSTEIN (New York, N. Y.): Dr. Necheles's ingenious hypothesis brings up a possible explanation both for the decrease in the resistance of the tissues to ulceration and the increase of the acid. His idea would explain both factors simultaneously.

I should like to discuss briefly the acid factor. I have demonstrated that in duodenal ulcer the psychic or nervous secretion, produced by the chewing of an orange, is very high as compared to normals.

There is a marked difference in this respect in duodenal ulcer and in gastric ulcer. It is well known that a high percentage of duodenal ulcer patients have hyperchlorohydria; gastric ulcer patients on the other hand have a low or normal acidity. This striking difference has to be explained. Either the two diseases are different or two different mechanisms may be involved.

Dr. Ivy has performed some interesting experiments in dogs. If he cut the sympathetics and gave a rough diet, he got marked hypermotility with a dumping action into the duodenum and duodenal ulcer. When the vagus was cut, stasis in the stomach occurred followed by a gastric ulcer. It would prove interesting to study the difference in constitution in both types of ulcer. We know that gastric ulcer rarely occurs in the hypersthenic stomach.

If you do a partial gastrectomy in a patient with a duodenal ulcer who has a high acidity before the operation, in approximately half of the cases free hydrochloric acid persists and recurrent ulcer occurs in 3% of these acid cases. If you add anterior vagotomy to the partial gastrectomy in duodenal ulcer patients who have a high acidity before the operation, you get an achlorhydria in nearly 100 per cent of the cases and no recurrences.

In sixteen out of nineteen cases who had this operation, i.e., vagotomy plus partial gastrectomy, performed by Dr. A. A. Berg, we found an achlorhydria which persisted throughout the follow-up period of 5 to 9 years.

Peptic Ulcer Emergencies

A Study of Massive Hemorrhages and Acute Perforations Treated During the Diagnosis of 916 Private Cases Suffering from Peptic Ulcer*

By

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A REVIEW of representative recent literature (2, 4, 6, 7, 8, 10, 11, 14, 15) shows that in patients admitted to large charity hospitals because of hemorrhage from peptic ulcer the mortality rate varies between 15 per cent and 30 per cent. Goldman's (15) recent report from the San Francisco General Hospital gives a mortality of 15 per cent.

A few variations of this mortality rate are noted: Finsterer (14) of Vienna, reports a mortality rate of 5 per cent following emergency surgery on all bleeding ulcers; Gordon-Taylor (12) believes that many patients should be operated upon during acute bleed-

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From The Mason Clinic, Seattle, Washington.

ing and reports a lower rate following operation than with medical treatment; Lahey expects a 5 per cent mortality from hemorrhage; and Hurst (13) reports a mortality of 4.8 per cent from Guy's Hospital; he states "the danger of hemorrhage from ulcer has been grossly exaggerated in a number of papers recently appearing in British Journals." Hurst feels that in private practice the mortality from hemorrhage is between 1 and 3 per cent.

The extremes of opinion seem to be shown by (1) Finsterer (14), who feels that immediate operation for bleeding ulcer is always indicated and that no case should be refused immediate operation on account of exsanguination, and (2) Hurst (13), who feels that operation is never indicated, or should be reserved for "very rare cases." In his series one case was operated upon and the result was fatal. Between these extremes are many opinions, but a review of articles shows that immediate emergency surgery is rarely undertaken. The idea is repeatedly recorded that cases which will result fatally cannot be separated by clinical evidence from those that will survive; and that surgical mortality is much higher than that from medical supportive treatment; hence, we should not increase mortality by emergency attempts at surgical control of hemorrhage.

Such wide variety of opinions has led us to investigate the private patients at The Mason Clinic and the Virginia Mason Hospital. Our Clinic consists of a group of men in private practice who exclude the fields of obstetrics and pediatrics.

This report is based upon the study of 916 patients on whom the diagnosis of peptic ulcer was made, using all ordinary methods for diagnostic study and laying great emphasis on clinical history and roentgenologic findings. As formerly reported (1, 3), we feel confident in a diagnostic accuracy approaching 95 per cent.

The Clinic has examined approximately 65,000 patients during the time these ulcer cases were collected, an average ulcer incidence of 140 per 10,000 (1.4 per cent). However, the incidence of acute perforation is approximately 9 per 10,000 (.09 per cent); of massive hemorrhage it is 5 per 10,000 (.05 per cent); and of fatalities from hemorrhage from peptic ulcer it is 1 per 10,000 (.01 per cent). These figures justify the frequent assertion that many busy general practitioners have never seen a fatal ulcer hemorrhage and hence consider that the mortality rate must be very low.

The 916 cases have been recently tabulated in great detail; and from them we have segregated those (1) with a history of previous gross hemorrhage, (2) with active massive hemorrhage and, (3) with acute perforation.

HISTORY OF HEMORRHAGE

I. One hundred sixty-two cases, or 18 per cent, have a history of previous hemorrhage. Less than half have had severe clinical ulcer symptoms, and in the large majority the gross hemorrhage has not been a critical affair. Not infrequently hemorrhage has been the first definite clinical symptom of ulcer that has made the patient consult a physician. Recurrent hemorrhages are frequently noted. A tabulation by age at the time of the first hemorrhage shows that 75 per cent of first gross hemorrhages occur under the age of fifty.

916 PEPTIC ULCER HISTORIES
162 Histories of Gross Hemorrhage
Mason Clinic

Severity of Ulcer History									
					I	37			
					II	51			88
					III	53			
					IV	21			74
Decade	1	2	3	4	5	6	7	8	
1st Hemorrhage	0	24	53	43	28	11	3	0	

916 cases diagnosed Peptic Ulcer

MASSIVE ACTIVE HEMORRHAGE

II. Massive active hemorrhage has brought thirty-six of these patients to the hospital, twenty-two with their first hemorrhage. These patients do not include all admissions with active bleeding, but only those that have had severe symptoms from loss of blood. The active massive hemorrhages have occurred in cases with relatively mild clinical histories in more than half; and have occurred in a relatively or absolutely quiescent period in the great majority. Yet in the six fatalities (18 per cent) which occurred from hemorrhage while in the hospital three were having severe ulcer pains. Two of the six patients died with their first hemorrhage.

Age seems to be the greatest factor in mortality from hemorrhage. Of thirty patients surviving active hemorrhage, twenty-two were under the age of fifty years. Of six fatal cases, three were under fifty years old, and two of these were surgical deaths not due to

MASSIVE ACTIVE HEMORRHAGE — PEPTIC ULCER
Mason Clinic (private cases)

36 Active Massive Hemorrhage		
Ulcer symptoms	Active	5
	Quiescent	31
Severity previous ulcer symptoms	I	5
	II	15
	III	10
	IV	6
Total mortality 18%	Medical	3
	Surgical	3

162 histories of gross hemorrhage (18%)

hemorrhage. Of six fatalities in the hospital from hemorrhage, four were due to loss of blood; and three of these patients were above fifty years old.

ACUTE PERFORATIONS

III. A few years ago we reported before this Society (5) our experience with acute perforations of peptic ulcer. Large series of cases suffering from acute perforation had been reported by various other

observers. General agreement is found that immediate emergency operation is indicated, that the operation within the first twelve hours carries a low death rate, and that closure of the perforation apparently is followed by a cure of the disease in many of the patients who survive operation.

We now have treated sixty-two perforations. Two-

ACUTE PERFORATIONS—PEPTIC ULCER
Mason Clinic—(private cases)

916 cases diagnosed Peptic Ulcer—	
62 Acute Perforations	41 during quiescent symptoms
	21 during active symptoms

4 only with previous diagnosis

thirds of acute perforations occurred during silent periods of ulcer symptoms. Massive hemorrhage has occurred at the time of perforation in only three instances. Four patients out of sixty-two had been previously diagnosed or treated for ulcer. Twenty-five were below fifty years of age, thirty-seven above fifty; and we are unable to say that the patient's age has made any definite difference in surgical mortality. The sex ratio was fifty-six males to six females, again showing the infrequency of acute perforation in women.

GENERAL CONSIDERATIONS

These findings have led to considerable thought in an attempt to recognize the clinical type of peptic ulcer that is likely to cause critical hemorrhage or to perforate.

Mann's studies on experimentally produced chronic duodenal ulcers of dogs are most enlightening. He finds two types of bleeding: First, in the healing of an ulcer the epithelium grows over the base of the ulcer, and is smooth and very loosely attached to the base — so loosely in fact that it is difficult without special precautions to demonstrate this epithelium at autopsy. The epithelium may be brushed off or even washed off under a faucet. In life this should be followed by bleeding in certain instances, a venous or granulation bleeding which should never cause critical loss of blood. Second, he finds that in an active ulcerating stage of experimental peptic ulcer the erosion may eat into the wall of an artery, technically known as *arrosion*, causing extensive or even fatal hemorrhage. Naturally Mann cannot evaluate the clinical subjective symptoms in the dog leading up to arrosion.

These two types of hemorrhage seem to us to offer a plausible hypothesis for what we see happen in certain patients. As already shown, the majority of recognizable hemorrhages occur in ulcer cases with milder symptoms; hypothetically it seems to us likely that these cases are milder because they are repeatedly and frequently healed. The "silent hemorrhage," so often seen and not so critical in younger people, occurs in a healed or healing stage. On the other hand arrosion bleeding should occur with active symptoms of ulcer. Hypothetically, silent hemorrhage should occur in a healed or healing stage and hence is likely to come at a time when the patient is not suffering clinical symptoms of ulcer. By contrast, if active symptoms are present at the time of hemorrhage, we should suspect arrosion and critical or fatal hemorrhage.

Actually we have found in our series that severe ulcer symptoms apparently precipitated massive hemorrhage in five instances, two of which were fatal. Arrosion, however, is clinically by no means confined to cases with active symptoms. Of thirty patients surviving critical hemorrhages, twenty-seven were relatively free from symptoms at the time that massive bleeding occurred. We have operated in two instances where a fatality seemed inevitable because of prompt recurrence of massive hemorrhage; and in both instances we feel that the operations were actually lifesaving.

The fatalities following surgery were all on cases treated for days, transfused repeatedly, and then operated. One death resulted from failure to control hemorrhage (age sixty-one), one from technical postoperative complications, and one from exhaustion with an acute postoperative psychosis. Finsterer feels that operative risk is greatly increased by delay for days of treatment and for transfusions, and then surgery undertaken before recovery of general health; our experience seems to coincide with his.

The most outstanding fact in this study seems to be that age is the first consideration as regards prognosis with massive hemorrhage; that any serious hemorrhage in a patient beyond fifty years old (and probably beyond forty-five) is a very dangerous symptom, nearly ten times as dangerous as in a patient under fifty years old.

Apparently a lesson may be learned from the Massachusetts General (7), where they believe that medical treatment is always to be given thorough trial in cases of massive hemorrhage — 138 critical ulcer hemorrhages treated with a 14.5 per cent mortality. Eight patients were, however, operated upon after "all hope had been lost for a spontaneous recovery," and all eight died. Manifestly that is not the way to handle such situations.

Acute perforations, according to our records, almost always occur (93 per cent) in those who have not even suspected ulcer or had symptoms serious enough to induce them to consult a physician or to take any kind of treatment. It seems clear that perforation of chronic duodenal ulcer through the anterior wall of the duodenum is far more common, and that such an ulcer produces very mild symptoms or none that are ascertainable. The usual perforation is essentially a "blow out," a very sudden and dramatic event. Only a small portion of acute perforations are the result of deep erosion and have massive hemorrhage from arterial bleeding from a branch of the pancreaticoduodenal artery in the posterior wall. Perforation of gastric ulcer is more likely to take place during active ulcer symptoms.

VITAL STATISTICS FROM SEATTLE

We have not found in current literature any clinical deductions regarding hemorrhage or perforation based on vital statistics. It seemed to us likely that efficient health department records might give valuable information.

In Seattle we have the King County Hospital with a tributary city and county population of nearly 500,-

000 people. The Hospital mortality rate during 1935 and 1936 from massive gastric hemorrhage from peptic ulcer was 20 per cent, and the Hospital has approximately half of all deaths from peptic ulcer recorded in the city and county. They have an active

VITAL STATISTICS FROM SEATTLE (400,000)
124 Deaths from Peptic Ulcer
Years 1935-1936

	Operated	Medical
62 Acute Perforation	34	28
42 Massive Hemorrhage	11	31
20 Other Causes	10	10
	55	69

54 autopsies

autopsy service and for this reason we feel sure that vital statistics from Seattle are fairly accurate, and are proven by nearly 50 per cent autopsy records.

With the cooperation of the Seattle Health Department we have reviewed all death certificates for the years 1935 and 1936. These vital statistics show that during two years massive hemorrhage from ulcer was the assigned cause of death in forty-two instances, and acute perforation as cause of death in sixty-two instances, out of a total of 124 deaths attributed to peptic ulcer. The diagnosis was substantiated in fifty-four patients by autopsy.

The vital statistics show that thirty-one patients died without surgical interference for hemorrhage, and eleven patients died following surgical interference. Of the forty-two deaths, eight occurred below the age of fifty and thirty-four above the age of fifty.

The vital statistics also show that of sixty-two perforations, twenty-eight died medical deaths, thirty-four died following surgical intervention. Twenty-four of these patients were under fifty years old and thirty-seven were above fifty years old.

Interesting deductions may be made because, as we

VITAL STATISTICS FROM SEATTLE
104 Deaths from Emergencies of Peptic Ulcer

Decade	2	3	4	5	6	7	8	9
42 Hemorrhages								
31 Medical			6	7	11	4	3	
11 Surgical	1		1	1	5	3		
Totals	1		7	8	16	7	3	
38 males — 4 females								
62 Perforations								
28 Medical		3	9	5	5	4	2	
34 Surgical		3	10	19	1	1		
Totals		6	19	24	6	5	2	
53 males — 9 females								

have shown, gross hemorrhage is very much more frequently found under fifty years old, yet the death rate from hemorrhage in older patients is ten times higher. No such statement can be made in connection with age and acute perforations.

Ten patients died, according to death certificates, following operation in which neither perforation nor hemorrhage was recorded, and ten died from medical conditions which presumably were considered by the attending physician as the immediate cause of death, with peptic ulcer as the chief cause of death.

SUMMARY

Our studies then seem to indicate that in private practice in Seattle the immediate mortality rate from massive hemorrhage from peptic ulcer is 18 per cent—if all deaths are recorded—or 11 per cent if we exclude two postoperative deaths not due to hemorrhage. Much the greatest mortality factor is age, for deaths from hemorrhage under fifty years old are relatively rare; though our records show that most hemorrhages occur in patients under fifty.

Arterial disease must be the explanation of the remarkable importance of the age factor in the prognosis of massive hemorrhage. Younger arteries will contract much more efficiently; in older people with marked sclerosis it may be impossible for the artery to contract sufficiently to promote clotting and stop the hemorrhage. This probability may account for the hesitancy on the part of surgeons in operating on cases of massive hemorrhage, and in their uncertainty as to what procedure is best undertaken at operation. However, surgical procedures are not part of this discussion.

It would seem that conservative treatment is always to be instituted. However, if the hemorrhage is in an older person, and particularly if it recurs promptly in the presence of active ulcer symptoms, one should assume that arrosion has taken place. The mortality with such cases is very high—from the literature and from our experience about 50 per cent. *Prompt* expert surgical intervention will undoubtedly reduce this extraordinary death rate—yet intervention a few days later because of failure to improve with medical treatment, gives an average surgical mortality of 47 per cent in seventy-two cases, as shown by six representative institutions (2, 7, 8, 10, 11, and loc cit).

CONCLUSIONS

1. In private practice in Seattle the hospital mortality of massive peptic ulcer hemorrhage is 18 per cent—and if we exclude deaths not due to loss of blood, it is 11 per cent.
2. King County Hospital in Seattle shows a mortality rate of 20 per cent on admissions for massive ulcer hemorrhage.
3. King County Vital Statistics and our figures in private practice there show that age is the greatest factor in mortality from hemorrhage.
4. Most severe hemorrhages are likely to occur during quiescent symptoms of an ulcer.
5. "Bleeding ulcers don't perforate; and ulcer perforations don't bleed."
6. The majority of histories showing ulcer hemorrhage relate a relatively mild severity of clinical symptoms of ulcer.
7. Severe symptoms of ulcer leading to hemorrhage strongly suggest arrosion, and in an older person may indicate a life-saving emergency operation.

8. Emergency surgery has its place in the treatment of certain cases of massive gastric hemorrhage before "all hope is lost for spontaneous recovery."

9. The large majority of acute perforations occur during quiescent symptoms—and in patients who have never had severe ulcer symptoms.

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The Differential Diagnosis of Gastro-Intestinal and Cardiac Disorders*

(The Alvarez Lecture)

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LIDDELL and Scott's Greek Lexicon gives the following definitions *Kardia*, heart, stomach, and *Kardiakos*, of the heart or stomach, dyspeptic. No wonder we have been confused ever since.

Neuburger of Vienna, the medical historian, in writing of the opinions of the Greeks and Romans in Galen's day and before quotes from their works as follows: "The sense of hunger depends upon cold and dryness and has its seat in the 'cardiac orifice' (the expression cardia or stomachos stands for the esophagus; the cardia was supposed to be very rich in sensory nerves and thus the starting-point of many morbid conditions)." Neuberger goes on to say that "the so-called 'morbus cardiacus'—frequently mentioned by the ancient medical authors, and probably a neurosis—was considered by Galen to be an acute illness originating in the stomach."

The opinions held through the middle ages are summarized at their termination by the great physician Fernel who in 1554 wrote his masterpiece of medicine. At the beginning of Chapter III of the sixth book of the section on pathology and symptoms Fernel said (I shall give the literal translation): "Many symptoms vex the ostium at the beginning of the stomach. Some of these result from the fact that this structure is endowed with an extraordinary degree of sensation and is connected with great affinity to the principal parts of the heart and to the brain. To these other organs indeed, it is generally agreed, it may communicate its troubles and provoke them in various ways: the heart to cause swooning, syncope, and pain which has been labelled cardialgia; the brain to cause lethargy, catalepsy, brooding, unsociability, melancholy, and delirium, the reasons and causes of all of which are adequately explained thereby." Fernel also said that palpitation and abnormalities of the pulse may be caused by indigestion, in particular excess of food or drink.

In 1749, Senac, physician to the court in Paris wrote "The stomach is one of the commonest causes of palpitations; but this cause is not always an immediate cause or one acting on the heart without other influences; it is sometimes only an incidental cause. If there is, for example, a lesion in the ventricles, in the auricles, in the vessels, or in some other viscera, if that lesion by itself causes palpitations, the stomach will be able to activate that other cause. When it is filled, for example, it pushes up not only the diaphragm and bothers the respiration but it also compresses the belly and the aorta. . . .

"But the nerves too can be put into action by the stimulation which follows the filling of the stomach"—and may induce palpitation. Also indigestion and bad food and gas can induce palpitation. Belching and passing wind may give quick relief.

Senac went on to say that certain foods may cause palpitation. Coffee may do so. "I know a man who is so attacked when he eats lentils; he resembles in this respect Malpighi whose heart was agitated when he ate peas or beans. Simon Pauli reports that he was affected by palpitations in the autumn when he ate raw apples." . . . "The intestines produce palpitations just as does the stomach; such symptoms arise sometimes after violent purgation. . . . Some persons feel violent beating in the region of the heart when the belly is compressed and are relieved when it is free. . . .

"Among the affections of the intestines which cause palpitations we can place hemorrhoids. . . .

"The liver, which is one of the great organs of the animal machine can without doubt excite palpitations. Its lesions may cause dyspnea and often give pain in the region of the clavicles and in the back and front of the chest. . . .

"The spleen was regarded by the ancients as the principal cause of palpitations; it was, according to them the seat of melancholy. The black blood, to which they gave this name, was formed, they thought in this viscerum whose use was unknown." Senac ended this discussion by noting that Willis more recently had discarded this idea but had blamed the splanchnic nerves instead.

In 1761 Morgagni had no knowledge of any direct relationship between pathological structural changes in heart or digestive tract but he did cite the case of a very old man who showed at autopsy both gall stones and an unsuspected calcified stenosed aortic valve.

Finally, to illustrate the very modern point of view that was held by James Hope of London, 105 years ago I shall read from the introduction of his important "Treatise on the Diseases of the Heart and Great Vessels."

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"Again, there are few more common and certain exciting causes of palpitation and difficulty of breathing in disease of the heart, than derangement of the stomach. What happens to the patient in this case? Tracing the attack, in perhaps every instance, to a dyspeptic fit, he naturally concludes that the latter is the cause: that it is 'all indigestion.' 'Good air and plenty of exercise' are the remedies recommended: the result is an apoplectic seizure. The circumstance that before the introduction of the new mode of exploring diseases of the heart (auscultation), they could rarely be detected in their early stages, contributed to the error in question. For, as patients frequently recover from the early stages, the recovery was regarded by those who assumed this class of diseases to be incurable, as a proof that the affection was merely dyspeptic. Hence dyspepsia acquired the reputation of producing certain symptoms, particularly in the head, which are in reality foreign to it, being exclusively the results of a co-existent disease of the heart.

"There prevails another error, the converse of the above—that of mistaking nervous, or really dyspeptic palpitation, for disease of the heart. The frequency of cases of this kind, especially amongst men of studious habits, (and more particularly, I have noticed, among those of my own profession), is truly surprising; and, as it has always been considered difficult, and by many impossible to distinguish the two affections, the alarm created is sometimes distressing. Having thought this subject of so much importance as to demand a separate article, I shall here only say, that, so far as my own experience enables me to judge, the discrimination may be made with ease and certainty."

"There is scarcely a disease of the heart, accompanied with obstruction of the circulation for any considerable period, which is not productive of enlargement of the liver, and, sooner or later, of its ordinary consequence, abdominal dropsy. Yet there are few common facts in medical science less generally known than this intimate connection between the heart and the liver. The dropsy is ascribed to the latter; the treatment extends not beyond this organ; the unknown cause continues to reproduce its effect, and the patient, if he obtain relief at all, only obtains it to undergo a speedy relapse."

In recent years considerable advance has been made in the localization of activity of and sensation from the gastro-intestinal tract through the pioneer work of Walter Cannon and Walter Alvarez, in whose honor this lecture is named, and also through the work of your president, Chester Jones, among others. Among these studies has been the demonstration, particularly by Cannon, of the important effect of emotions on the action of the gastro-intestinal tract associated reflexly with disturbance of other organs especially the heart, but we have still much to learn about the details and inter-relationship of both cardiovascular and gastro-intestinal symptoms.

The differential diagnosis of gastro-intestinal and cardiac disorders is a subject of never-ceasing interest and importance. In the accumulation of experience one goes through a cycle of changing impressions. I can recall the assurance with which I started my own experience. There were handy rules to differentiate heart disease from stomach trouble and gall stones. But it was a time when we were acquiring much new knowledge and some of this was based on the errors we were making. I shall never forget being called in the summer of 1920 to see an elderly surgeon who was found to have an acute pericarditis, for some unknown reason complicating an attack of severe prolonged epigastric pain which had been diagnosed by himself and his medical friends as being the result of acute cholecystitis. Characteristic coronary T waves in electrocardiograms a few weeks later were ignored. It is easy now in retrospect, of course, to diagnose extensive myocardial infarction secondary to coronary thrombosis. Errors similar to that one shook our confidence in those days but gradually we regained our assurance in the course of the next decade by dint of careful analysis of clinical, postmortem, electrocardiographic, and X-ray studies. Several years ago we again felt masters of the situation but a few humbling experiences since then have indicated the folly of a cocksure attitude in doubtful cases, even with all the resources at our command at the present day. There are almost certainly rare cases in which a clear differential diagnosis between cardiac and gastro-intestinal disorders is impossible and likely to remain so, but our diagnostic acumen is still so amenable to improvement that it is bound to improve with further experience.

To illustrate some of the more common, important, and difficult problems in this field I shall cite briefly several cases that I have myself encountered.

Case 1. Esophageal pain or coronary insufficiency—which? A salesman, 37 years old, nervous and a heavy smoker, came to me complaining that for about ten months he had been occasionally troubled by a substernal burning sensation radiating equally to both shoulders, never very severe, lasting fifteen to thirty seconds and subsiding when he belched gas after taking a drink of water. This sensation usually came on when he was sitting quietly at home in the evening shortly after dinner, about once in two or three days. It never was induced by effort; in fact, exercise such as golf, stair-climbing, and even running seemed to help him. The reduction of tobacco from 20 cigarettes or more a day to 2 or 3 was attended by complete relief of his trouble. Otherwise he had been well. Physical examination, electrocardiogram, and fluoroscopic examination of the thorax revealed no abnormalities whatsoever. Much gas was noted fluoroscopically in the stomach and colon raising the left leaf of the diaphragm.

DISCUSSION

This story can be duplicated time and time again. Usually it is evident at once that the trouble lies in the gastro-intestinal tract and not in the coronary circulation, but occasionally careful study is needed clearly to determine the etiology, and rarely an erroneous diagnosis of angina pectoris due to coronary disease is made. The history alone usually suffices for diagnosis, but it is sometimes very helpful to have also electrocardiographic and roentgenological evidence.

There are three more common types or circumstances of esophageal pain. The most common is probably "heartburn," a burning sensation like that described in the patient noted above and due in many cases probably to the eructation of acid gastric juice or contents into the lower esophagus. The second is actual spasm of the esophagus at its lower end, the so-called *cardiospasm*, which may sometimes be seen roentgenologically when barium is swallowed. The esophageal peristaltic waves may be disturbed in their function, prolonged, or even reversed. The globus hystericus has been ascribed to the meeting of contraction waves traveling in opposite directions at the upper end of the esophagus. The third type of esophageal pain is the result of the pressure

of air or food entrapped in the esophagus as in aerophagia. Here there is the combination of the pressure of the esophageal contents and the spasm of the esophagus above or below. Air swallowing or cribbing is very common and may be observed in operation with relief of discomfort on belching up the air or in passing it on into the stomach.

In the differential diagnosis of coronary and esophageal pain the history of the occasion of the pain is of chief importance. The position and radiation of esophageal and gastric pain is likely to be the same as that of angina pectoris and even its character may be similar; as a rule however the pain of coronary insufficiency is that of a heavy oppression or choking (as indicated by the word angina itself, which means strangling) while gastric or esophageal pain is more often burning or sharp and is well characterized at times by the designation "heartburn." Either pain may be epigastric or low, intermediate, or high in position behind the sternum. Coronary pain is more likely to radiate into the left arm but often it doesn't radiate at all. Effort is almost invariably the exciting factor of the pain of coronary insufficiency, while eating is more commonly the occasion for the occurrence of esophagospasm or cardiospasm or heartburn. Also the excessive use of tobacco is especially likely to favor the occurrence of esophageal or gastric pain. Excitement may induce either type of pain, gastro-intestinal or coronary. A common accompaniment of the substernal pain of gastric origin at its termination is the belching or eructation of gas that attends the release of the spasm of the lower end of the esophagus or of the cardiac sphincter of the stomach.

Three further considerations are of great importance: First, the nitrites tend to relieve the pain of esophagospasm or cardiospasm as well as that of coronary insufficiency, though as a rule more slowly, and so are not a satisfactory therapeutic test for differential diagnosis. Second, quite often coronary insufficiency and esophageal irritation or irritability coexist in the same individual. The patient may have angina pectoris on effort and esophageal pain or "cardiospasm" after meals or an attack of angina pectoris may induce "cardiospasm" sympathetically with almost simultaneous relief of the two mechanisms by resting or nitrites. When such simultaneous occurrence and relief of the two conditions occur the case may be difficult of analysis; it is doubtless the apparent relief of angina pectoris by the belching of gas that has caused confusion and even led to the idea that the pain of coronary insufficiency is in reality wholly due to the "cardiospasm" that is induced reflexly by it. An especially observant patient who has both kinds of pain can usually distinguish between the two: this fact, the occasion of the occurrence of the pain, its character, and the fact that atropin or belladonna tends to prevent "cardiospasm" but not angina pectoris indicate that they are in fact two separate conditions. And third, an increased heart rate and more forceful heart action following food or certain drinks, especially coffee, tea, and alcohol, may readily be interpreted by the patient as painful; it tends, however, to be precordial aching rather than substernal oppression or burning.

We must remember that there are a number of different causes for pain in any part of the chest, superficial and deep. This includes the retrosternal region which is too often regarded by each specialist as his own particular province, by the cardiologist as the site of the angina pectoris of coronary insufficiency, by the gastro-enterologist as the site of esophageal or gastric pain, and by the pulmonary expert as the site of the pain of tracheal and bronchial disease or of mediastinal tumor. Almost any pathological change in the mediastinum can cause retrosternal pain which may or may not radiate to arms, back, or neck.

Before leaving this discussion, mention should be made briefly of the infrequent cases of esophageal ulceration, tumor, or diverticulum with pain high up substernally, closely resembling in site the angina pectoris of coronary insufficiency and likely to be wrongly diagnosed. The pain is, however, more related to eating than to exertion and more prolonged in its attacks. When in doubt careful fluoroscopic observation of the esophagus during the swallowing of barium and esophagoscopy should be carried out. Other causes of obscure retrosternal pain are that occasioned by a central diaphragmatic hernia and that occurring on swallowing by the esophageal obstruction caused by a congenital right sided aortic arch or anomalous right subclavian artery.

Case 2. Coronary disease with angina pectoris complicated by aerophagia and cardiac neurosis. A housewife, 55 years old, enters the hospital on April 13, 1937, with a history of having first noticed substernal oppression three and a half years ago when walking in the evening after eating. Associated with this there was "indigestion" characterized especially by the belching of gas. Upon resting and upon belching gas the substernal discomfort was relieved within a few minutes. One year later her mother died as a result of angina pectoris. Shortly after this the patient began to notice pain in the upper anterior chest in association with an increased amount of distension from gas and of belching of gas. The pain occasionally radiated to the left arm and to the back of the chest on the left side near the scapula. Eight months before her entrance to the hospital she had a prolonged attack of substernal oppression and precordial pain, lasting for hours, and attended by prostration. Ten weeks before admission, after the removal of a corn beneath the nail of the right second toe, she began to have pain in the toe with slow healing, and later infection. She had noticed some numbness in the right foot for a year. Slight hypertension and diabetes had been discovered at the age of 43, but the glycosuria was readily controlled by moderate restriction of diet.

On examination the patient was found to be slightly obese. There were no abnormalities expect for very slight hypertension, the blood pressure ranging from 145 to 160 and about 90 diastolic. There was a decrease in the arterial pulsation in both legs. There was no evidence of congestive failure.

The various laboratory tests were all normal except for the electrocardiogram which showed low, diphasic T waves in Lead 1, and abnormal T waves in the precordial or chest lead, X-rays of the legs which showed extensive calcification of the blood vessels of the legs and ankles, and a high blood sugar.

Under observation it was evident that the patient, especially when nervous, was very much inclined to gulp and belch gas, complaining of the discomfort in the chest therefrom.

DISCUSSION

This patient is a good illustration of the combination of coronary disease with slight angina pectoris complicated by aerophagia and cardiac neurosis. Her

coronary symptoms had subsided completely by the time of her entrance to the hospital for study, but her aerophagia and the discomfort therefrom had become more marked and were easily detected. The only abnormalities on examination were the electrocardiographic evidence of coronary disease and the X-ray evidence of peripheral vascular arteriosclerosis. These findings, however, are of great importance in the complete study of a patient suspected of having cardiovascular disease.

Case 3. Circulatory collapse incident to gastro-intestinal disease. A professor, 49 years old, always highly nervous and recently under severe mental strain, had been seized five days before I saw him by very severe epigastric pain which kept him awake all night and which was followed by tarry stools. He had had heartburn and other evidences of indigestion for twenty years or more and roentgen ray examination showed a small duodenal ulcer. He improved rapidly on Sippy powders and diet but late the night before I saw him while he was listening to the radio he was seized by a desire to go to the stool. He went to the bathroom and had a copious bowel movement. In fear he looked to see if it contained blood. When his fear was confirmed he grew greatly alarmed and at once began to feel faint. He dragged himself back to bed and collapsed. There his wife found him semicomatose and a doctor who was summoned discovered him in a cold sweat with impalpable pulse at the wrist and a very slow heart rate of about 20. After a few minutes he recovered and the next morning when I examined him I found nothing at all wrong except for the story of the recent bleeding from the gastro-intestinal tract. An electrocardiogram showed no heart block. The important history was elicited of an exactly similar collapse twelve years before after an indigestible meal late at night.

DISCUSSION

This case illustrates the frequent occurrence of circulatory depression that may attend any illness or fright, whether incident to gastro-intestinal trouble, or to heart disease (for example, coronary thrombosis), or to other complaint. There may be a marked depression of the sinoauricular nodal pacemaker as well as of general vascular tone without any organic heart block at all, despite the bradycardia.

Case 4. Peptic ulcer diagnosed as coronary disease with angina pectoris decubitus. The wife of an army officer, 46 years old, had begun to have nocturnal attacks of severe sharp low substernal pain, nonradiating, attended by nausea, and lasting several hours at a time, five and a half months before I examined her. This had recurred nightly for several weeks but finally subsided after bed rest. For some months thereafter she felt fairly well, being free from pain. Then she overdid in preparing for Christmas and the nocturnal attacks recurred. Ten days later when I examined her there was evidence of hypertension (systolic blood pressure 165 and diastolic 120) and slight cardiac enlargement. The electrocardiogram was essentially normal and the Wassermann and Hinton reactions were negative. Gastro-intestinal roentgen ray examination revealed the presence of a peptic ulcer and treatment by rest and diet was instituted. She has been free from symptoms since this treatment was started. Her blood pressure has continued to be moderately elevated.

DISCUSSION

Although angina pectoris decubitus is possible in a middle aged woman with hypertension it is very unlikely in the absence of a previous history of angina pectoris on effort or of evidence of luetic aortitis. Also of course paroxysmal angina pectoris is at once excluded by the duration of the attacks of pain; coronary thrombosis which might explain the duration of an individual attack would not recur night after night, leaving her in fair comfort and health in the daytime. The electrocardiogram too would almost certainly have shown evidence of coronary disease had the latter been the occasion of such frequent severe pain. Fortunately the treatment of the peptic ulcer is about as suitable as anything we know of for the treatment of the hypertension and its effect on the heart.

Case 5. Gall stones erroneously diagnosed as coronary thrombosis or pulmonary embolism. An obese housewife, 60 years old, had always been well until her present illness except for pneumonia at the age of 29 and varicose veins for many years culminating in an ulceration in the summer of 1935, one and a half years before I first saw her; this ulceration had finally healed in the course of some weeks. On December 26, 1935, she was awakened in the middle of the night by a very severe choking pain across the front of the chest radiating into the neck and left arm, attended by nausea and vomiting, lasting for hours, requiring morphine, and followed by several days of fever. She gradually improved and was fairly well through the spring. In June, 1936, she had a similar attack with vomiting. Through the summer there were several milder spells and then in October another very severe attack with collapse. She then remained in bed nearly two months and was only just beginning to sit up in January, 1937, when I first saw her, a year after her first attack of pain. There had been two mild spells in the fortnight before my examination. I found no abnormalities of heart, lung, abdomen, or blood pressure. The electrocardiogram was essentially normal. A few weeks later another severe attack occurred with persistent vomiting and tearing substernal pain. There was marked tenderness with spasm in the epigastrium. Bile appeared in the urine the next day, and the stool was clay colored. The diagnosis was now obvious.

DISCUSSION

Here is a good example of the difficulty of the early differential diagnosis of gall bladder disease and coronary thrombosis. In the first place the sex and absence of previous angina pectoris and hypertension favored the former condition. Later the constant occurrence of vomiting with the attacks, the frequent repetition of the pain, and the absence of characteristic electrocardiographic findings practically ruled out coronary thrombosis. At one time the repeated attacks of chest pain and the old history of varicose veins and phlebitis suggested the possibility of recurrent pulmonary embolism but there was nothing to support the diagnosis. Nausea and vomiting always favor the diagnosis of trouble below the diaphragm unless they are induced by morphine given for the relief of pain or by excessive dosage of digitalis given because of real or fancied myocardial failure. Often these drugs are responsible for nausea ascribed to indigestion of some sort. Much better evidence than vomiting is that yielded by the occurrence of persistent hiccoughing. Obstinate hiccoughs may result from diaphragmatic pleurisy secondary to a large pulmonary infarct but it is far more common from irritation subdiaphragmatically and is exceedingly rare in coronary thrombosis. I have myself never encountered it as a complication of coronary thrombosis; the one time I did make such an interpretation I was in error, the chest

pain and absence of signs of trouble in the abdomen being caused by an unique position of a pus-filled gall bladder situated high, almost like an intrathoracic organ, under the right leaf of the diaphragm which had become inflamed by contact.

Case 6. Gastro-intestinal disease complicated by silent (?) coronary disease. A housewife, 54 years old, had had for many years an ill defined indigestion and for a few years a variable slight hypertension. Eight days before I was asked to see her she had had an attack of severe epigastric pain with nausea. Twenty-four hours later the pain had shifted to the right lower quadrant of the abdomen where there were tenderness and spasm. The temperature was 101 degrees and continued elevated for two or three days. The blood pressure was 150 systolic and 90 diastolic. A week later, on the morning of the day I examined her, while she was being prepared for appendectomy she had another attack of severe epigastric pain with pallor and a drop in blood pressure to 100 systolic and 50 diastolic. An electrocardiogram showed inversion of the T waves in the classical leads, upright T waves in the precordial lead, and a prolonged P-R interval of 0.21 second. The Q wave was present in Lead 4. The operation was postponed. Repeated electrocardiograms during the next few days showed no change. The epigastric pain subsided but some right lower quadrant tenderness persisted. Finally, thirteen days after my examination laparotomy was performed and an inflamed appendix was removed without incident. The abnormality of the electrocardiogram persisted. There was no more pain.

DISCUSSION

Here was a case of gastro-intestinal disease complicated by real heart disease which apparently was incidental, revealed by electrocardiogram. It is quite certain that the electrocardiographic abnormality and the underlying coronary disease were not produced by the acute appendicitis. It is true that gastro-intestinal disease, especially gall stones, may induce functional cardiac and general circulatory disturbances, especially premature beats, paroxysmal tachycardia (even in the form of auricular fibrillation), and vascular collapse but that it can actually and directly produce organic myocardial, endocardial, or coronary disease is extremely unlikely. Heart failure or angina pectoris or electrocardiographic anomalies may, however, be precipitated and perhaps for the first time brought to light by disease below the diaphragm but no more than by any other strain, and certainly not fundamentally caused thereby.

Case 7. Coronary thrombosis and "silent" gall stones. A surgeon, 41 years old in October, 1936, had been well except for a liver abscess following appendectomy in 1917, and pneumonia following influenza in 1929 until January, 1935, when he began to have mild substernal oppression on vigorous effort. This symptom increased in frequency and severity until March 20, when he was seized by a terrific substernal and bilateral arm pain lasting several hours and requiring morphine. Typical clinical and electrocardiographic evidence of coronary thrombosis ensued and he remained in bed three months. When I examined him in October, 1936, he was still incapacitated by the typical angina pectoris of coronary insufficiency. The electrocardiogram was still abnormal. A routine gastro-intestinal X-ray examination a few months before had revealed two gall stones and he asked if these should be removed. We advised against the operation, at least at that time. Further treatment of the coronary disease was recommended.

DISCUSSION

Gall stones are common and often silent. Only occasionally must they be removed. Operation always carries some risk and in the presence of serious coronary disease as in this patient it may kill. There is very little likelihood that the gall stones were a source of aggravation of the heart trouble in this particular case.

*Case 8. Paroxysmal tachycardia, wrongly interpreted as angina pectoris, the result of reflex irritation of the heart from gall bladder disease.** A 54 year old housewife entered the Massachusetts General Hospital on April 5, 1933, to have treatment for persistently recurring nocturnal heart attacks by paravertebral alcohol injection of the sympathetic nerve ganglia and rami. Five years before she had begun to be troubled by momentary attacks of sharp, shooting pain originating just over the heart to the left of the sternum and radiating across the chest to the right and occasionally up over the left chest, almost to the clavicle. These transitory pains were not associated with exertion but seemed to come more when she was resting after a hard day and in the evening when in bed. She consulted her doctor who gave her tablets of nitroglycerine for the attacks, which seemed to give relief. This was at the time of the menopause. Ever since then this trouble had recurred at intervals, more frequently during the few weeks prior to her admission to the hospital, when she also noticed almost constant heartache, some dyspnea on hurrying, and blueness of her fingers and lips. Her ankles seemed to swell slightly at the end of the day. Her doctor digitalized her but she said that she had to omit the drug because of her inability to retain it.

About one year before entrance to the hospital she was troubled by another and more important symptom, consisting of precordial and substernal oppression in attacks at night, awakening her and causing her to sit up, lasting for a few minutes at a time, and not responding quickly to nitroglycerine. On one occasion she was given morphine for relief. During the three weeks before entrance to the hospital these nocturnal attacks had increased in frequency and severity, and had been accompanied by a feeling of impending death, cold sweat, and rapid heart beat. She had, however, continued to do her housework as before.

Her past history revealed no important illnesses. She had six healthy children. Her mother and one sister had died of tuberculosis.

Physical examination showed a well developed and well nourished middle-aged woman with good color, normal breathing, no edema, and no abnormal neck pulsations. Her heart was normal in size, sounds, rate, and rhythm. There were no murmurs. The pulse rate was 80. The blood pressure varied from 154 to 165 millimeters of mercury systolic and from 90 to 100 diastolic. The lungs were normal.

Electrocardiogram showed normal rhythm, and total inversion of Lead 3.

X-ray examination showed some increase in the transverse diameter of the heart, which was recorded as greater than the long diameter.

The urine and blood were normal except for very slight albuminuria and slight secondary anemia. There was no bile in the urine. The stool was normal. The Hinton reaction was negative and the basal metabolic rate was minus 10 per cent.

On April 5, the day of her admission to the hospital, I

*This case has already been reported in "Errors in the Interpretation of Cardiovascular Symptoms and Signs. *"Annals of Internal Medicine*, 9:1703, 1936.

saw her for a few minutes and wrote the following opinion: "Brief questioning does indicate the apparent occurrence of severe angina pectoris (decubitus) dating back three weeks (mild for two or three years before that). Examination shows no abnormalities except for slight hypertension. Further study—more careful history, electrocardiogram, roentgen-ray, Hinton reaction—are essential before final diagnosis. Paravertebral alcohol injection may well be indicated but I would advise postponing it for a few days until studies are completed. Try amyl nitrate for attacks." The surgeon wrote the following note on the record: "I believe that this patient is a suitable case for paravertebral alcohol block as her cardiac pain is so severe and she is getting so little relief from her medical measures. The only difficulty is the bilateral nature of the pain."

On April 7, 1933, we questioned her more carefully, realizing how rare severe angina pectoris is in a middle aged woman with little or no hypertension and no story of substernal oppression on effort, and we gave the following verdict: "Further history this morning reveals the vitally important fact that rapid regular heart beating at more than twice the usual speed always accompanies the anterior chest discomfort and apparently precedes it. This is extremely significant for it changes the diagnosis from coronary disease with angina pectoris to paroxysmal tachycardia with little or no heart disease. . . . She is already better in here resting. Sedatives and quinidine sulphate (3 grains three times daily) will be much more likely to help her than any other drugs. I expect the Hinton reaction will be negative. For completeness we shall have a basal metabolic rate determination. Certainly there is no need at present for paravertebral alcohol injection unless the paroxysms grow very much worse and are refractory." One week later on the new therapy she was feeling very well, completely free of heart attacks. She was discharged from the hospital much improved on April 15.

Three months later, on July 3, 1933, she came to my office with no complaints except for very slight heart twinges for a second at a time on two days the previous week. She was taking quinidine. Examination including electrocardiogram and fluoroscopy showed nothing amiss except for slight hypertension (170 mm. systolic and 95 diastolic).

In October she reported the occurrence of a spell of racing of the heart lasting a half hour after a recent fatiguing day. She had omitted the quinidine but thereupon resumed it. She no longer was afraid of the attacks, they had become simply disagreeable. Her blood pressure was 155 systolic and 90 diastolic.

She continued in good health (with infrequent palpitation) except for a series of acute attacks of typical gall stone colic with vomiting from August to November, 1935, completely relieved by the uneventful removal of her gall bladder containing a large stone. She continued to have infrequent brief paroxysms of tachycardia up to the time of operation but none thereafter. The blood pressure continued to be slightly elevated (170 systolic and 95 diastolic on February 10, 1936). The electrocardiogram, including the chest lead, has been normal.

DISCUSSION

It is probable that in this case the gall stones were responsible for the paroxysms of tachycardia. It is unlikely that some other disturbance may have been the chief factor. Some of the precordial pain in these nocturnal attacks from which she suffered may have been due to the gall stones and not wholly to the discomfort from the paroxysmal tachycardia.

Case 9. Heart failure and cirrhosis of the liver. A strenuous fat lawyer, 63 years old, who had used alcohol to excess, was found to have considerable hypertension (blood pressure 180 systolic and 122 diastolic) at the time of acute congestive heart failure in July, 1932. Intense breathlessness had been followed by dependent edema. His liver was found to be somewhat enlarged. The heart rhythm was normal. After a long rest and digitalization he improved and continued in fair health for two years. Then in July, 1934, he became breathless again. Treatment relieved him but in February, 1935, he once more developed severe congestive failure following an acute respiratory infection. Gradually this yielded but in May intractable ascites appeared and he required abdominal paracentesis every three weeks. There remained little dependent edema. Because of the unusual situation this patient excited much interest. On examination in April, 1936, he showed a very large heart with diastolic gallop rhythm, accentuation of the pulmonary second sound, moderately loud precordial systolic murmur maximal at the apex, absolute arrhythmia at a heart rate of 72, blood pressure of 170 systolic and 105 diastolic, slight engorgement of the neck veins, soft edema of both lower legs, considerable enlargement of the liver with hard edge, and an abdomen much distended by ascites. The urine was normal, the Wassermann reaction was negative, and the electrocardiogram showed auricular fibrillation with a ventricular rate of 65, abnormal left axis deviation, and inverted T waves in Lead 1. Improvement followed a considerable restriction in fluid intake and the continuance of digitalis and diuretic therapy.

DISCUSSION

This case illustrates the deleterious effect that one abnormal condition may have on another. Although the hepatic cirrhosis might eventually have caused trouble itself its effect was certainly precipitated by the severe heart failure. Congestive failure alone would not have produced such obstinate ascites unless chronic mitral stenosis of high degree were present; there was no evidence of mitral stenosis here. Two other cardiac lesions can cause a preponderant obstruction of the portal circulation with obstinate ascites; these two conditions are tricuspid stenosis and chronic constrictive pericarditis. There was no indication of either of these conditions here. Cirrhosis of the liver as an uncomplicated cause of ascites is not attended by engorgement of the neck veins, that is, an increase in systemic venous pressure. When there is the combination of preponderant ascites with overfilled neck veins we must look for one of the four conditions mentioned above: (1) either the combination of cirrhosis of the liver and congestive heart failure as in Case 9, or (2) high grade chronic mitral stenosis, or (3) tricuspid stenosis, or (4) chronic constrictive pericarditis.

Case 10. Upper abdominal pain due to liver enlargement secondary to mitral stenosis with right ventricular failure. A housewife, 38 years old, with rheumatic heart disease, mitral stenosis and auricular fibrillation of long standing, complained of a new symptom coming on during the three years prior to my examination of her in September, 1932. This symptom consisted of fullness and aching in the upper abdomen especially on the right side. Physical examination showed a woman somewhat overweight, with slight dyspnea, and engorgement and pulsation of the cervical veins in the upright position. There was clear evidence of mitral stenosis with auricular fibrillation and considerable enlargement of the heart. There were moderate enlargement and tenderness of the liver. The heart rate was 110. The blood pressure was normal. The electrocardiogram showed auricular fibrillation with

slight right axis deviation and inverted T waves in Leads 2 and 3. Fluoroscopic examination showed a very large, mitral shaped heart.

After rest and full digitalization she improved a good deal. There was less congestion of the abdomen.

A year and a half later she reported again complaining of having been much worse with increased congestion of the abdomen with some nausea and vomiting. Rest and diuretic therapy helped somewhat but because of the persistence of her marked limitation of reserve she underwent the operation for total thyroidectomy in February, 1934. Following the operation she improved rapidly, and in the next few weeks lost all sense of congestion in her upper abdomen. Her heart action was better and the liver was distinctly smaller. Her appetite was good. She continued in improved health with less evidence of engorgement of the liver which was responsible for her abdominal discomfort and fullness and nausea, during the next two years.

Finally, in the spring of 1936, she failed rapidly with congestive failure and died May 27, 1936.

DISCUSSION

In this patient the failure of the right ventricle was undoubtedly responsible for the engorgement of the liver and gastro-intestinal tract causing her discomfort. When there was relief of this failure there was also relief of the symptoms of abdominal discomfort and anorexia and nausea. It is in such cases that it is often difficult to know whether the abdominal discomfort and nausea may be the result of too much digitalis or too little. All the evidence available, including the electrocardiogram, is essential in the analysis of the problem. Besides the evidence and symptoms of the congestion of the liver and stomach, there sometimes may be associated with the congestion ulceration of the stomach, either fresh or recurrent due to the chronic congestion, and also hemorrhoids resulting from chronic congestion of the rectum.

Case 11. Liver enlargement and ascites due to chronic constrictive pericarditis. A healthy, active Irish lad, 12 years old, began to notice prominence of his abdomen three months before our examination. This abdominal swelling had slowly and steadily increased and recently had been so extensive that it had extended into his flanks. He had been active despite this and had had no shortness of breath or pain. There was no jaundice or urinary symptom. Four days before admission to the hospital his abdomen had been tapped, and straw colored fluid was removed. X-ray examination at that time showed calcification of the pericardium.

His father died of tuberculosis three months before the patient was born. His mother was living and well.

In the past he himself had had pneumonia at the age of 4 when he was critically ill for four weeks. He had measles, mumps, and chickenpox between the ages of 4 and 6. His tonsils and adenoids had been removed at the age of 2.

Physical examination showed a well developed and nourished boy, greatly put out at having to enter the hospital. There was slight general adenopathy. The chest flared at the costal margin to meet the protuberant abdomen. The lungs were clear. The heart was normal in size, and did not shift with change in position. There were no murmurs or thrills. The pulmonary second sound was loudly reduplicated. The pulse was regular at 90. The blood pressure was 90 systolic and 60 diastolic. The veins of the neck, arms and upper chest were dilated. The respiratory rate was 20. The abdomen was distended. The liver edge was felt three fingers below the costal margin, nontender. There was shifting fluid dullness. There was no edema of the legs. The reflexes were active. The respiratory rate was 20.

The blood was normal except for slight anemia, and clear reduction of the serum protein to 4.8 per cent. All other laboratory tests were normal except for slight reduction of the liver function and abnormality of the T waves in the electrocardiogram. The T waves were very low in Lead 1, diphasic in Lead 2, and slightly inverted in Lead 3. X-ray examination of the heart showed the measurements at the upper limits of normal, with a lateral area of calcification extending around the entire lower half of the heart. The lung hilus shadows were slightly enlarged, and there was slight thickening of the axillary and apical pleurae.

He entered the hospital June 30, 1933. On July 7, salyrgan intravenously resulted in a fair diuresis with the loss of two pounds.

On July 12, Dr. E. D. Churchill performed a pericardial resection, cutting away thick, hard pericardium over the anterior surface of the ventricles and over the right auricle to the cavae. Most of the diaphragmatic pericardium was removed.

There was an uneventful convalescence after the first two or three days, which were somewhat stormy. Then came a spontaneous diuresis beginning about the 7th day, and continuing for twelve days, at which time he was entirely free from evidence of surplus fluid. He has been perfectly well since this operation with no evidence of increased venous pressure; he is now fully active.

DISCUSSION

This case is an excellent illustration of congestion of the liver due to chronic constrictive pericarditis preventing the blood from entering the heart in sufficient amount. The onset was insidious. There was some discussion at first as to the probability of the diagnosis of primary cirrhosis of the liver. The factors which established the definite diagnosis were the accompanying engorgement of the neck veins, that is, the increase in systemic venous pressure, and the abnormality of the electrocardiogram, which are not found with an uncomplicated cirrhosis of the liver, and of course in addition the X-ray evidence of calcification of the pericardium. However, the diagnosis can easily be established without the X-ray; furthermore, it is to be noted that X-ray evidence of pericardial calcification is sometimes obtained without any constrictive pericarditis or liver enlargement or ascites.

Case 12. Jaundice due to extensive pulmonary infarction complicating rheumatic heart disease with mitral stenosis, auricular fibrillation, and congestive failure. A housewife, 49 years old, known to have had rheumatic heart disease with mitral stenosis and slight aortic regurgitation for many years entered the hospital because of recurrent rheumatic infection, arrhythmia consisting of paroxysmal auricular fibrillation and flutter, and congestive failure. There were associated attacks of chest pain and dyspnea with clear indication of recurrent pulmonary infarction, now in one lung, now in the other, and now in both. She grew much sicker, entered the hospital, and there developed jaundice, though not of high degree. Under full digitalis therapy, oxygen, and morphine she slowly improved but was still desperately ill. To the surprise of all concerned she gradually recovered, and has been in excellent health during the last year, although she

still shows clear evidence of the rheumatic heart disease and mitral valve involvement.

DISCUSSION

The point of particular interest in this case is the fact that jaundice may rarely complicate heart disease without primary disease of the digestive tract. It is quite likely that three factors played a role simultaneously in the production of the jaundice in this patient: one of these was the damage to the liver resulting from the rheumatic infection past and present. More and more evidence of this is being revealed in rheumatic fever studies at the present time. The second factor is congestive failure which adds to the burden of the already damaged liver, and finally the third factor, which is the precipitating one, is that of pulmonary infarction which adds to the blood stream a surplus of blood pigment, at the time of resolution of the infarct, which cannot be taken care of by the inefficient liver. This results in hematogenous jaundice.

Although the symptom of jaundice is rare in cardiac cases, its possibility should be borne in mind and the condition should not be interpreted as obstructive jaundice, unless there is clear proof thereof.

Case 13. Coronary thrombosis erroneously diagnosed acute indigestion. A clergyman, at the age of 48 years, had an attack of severe epigastric pain radiating substernally, and a little into both arms equally, lasting several hours, requiring morphine for relief, and attended by vomiting after the morphine injection. A diagnosis of "acute indigestion" was made and he remained in bed one week. Three years later he had a similar attack awakening him at night. A third spell of "indigestion" came eight years after that and finally a fourth just prior to my examination another four years later when the patient was 63 years old. All four attacks were almost identical. The clinical course of the fourth attack and the electrocardiogram were typical of coronary occlusion with myocardial infarction. The patient survived for another nine years and finally died of congestive heart failure more than twenty-four years after his first attack. His heart at autopsy showed extensive coronary occlusion and the scars of multiple infarcts.

DISCUSSION

I have included this case of coronary thrombosis because of its importance despite the fact that nowadays such an error is made much less often than ten years ago. In fact, the diagnosis of coronary thrombosis is made too often now. Nevertheless, every few weeks I still encounter acute coronary occlusion that at its onset was not recognized. The value of the electrocardiogram in such acute cases cannot be overemphasized.

Here it is appropriate to say a word about the so-called abdominal angina (angina abdominis). Coronary pain may be epigastric in position whether paroxysmal in type or due to coronary thrombosis, but otherwise the term as applied to heart disease is unwarranted. It is true, of course, that disease of the abdominal aorta either in the form of a dissecting aneurysm or of a large obstructing sac, and occlusion of lesser arteries in the abdomen can give rise to severe prolonged abdominal pain, but such pain is not comparable to that of angina pectoris except perhaps in rare cases of partial vascular occlusion; such cases need further study.

Thus, pain, collapse, nausea, jaundice, liver enlargement and other physical signs, and X-ray and electrocardiographic abnormalities are all symptoms and signs that must be carefully evaluated in the differential diagnosis of cardiac and gastro-intestinal disorders. A careful history is the first essential and generally establishes the diagnosis. Pain and collapse, and liver enlargement and tenderness may attend either of the two groups of diseases, but it is usually possible easily to analyze the difference. Nausea, vomiting, hiccoughing, and jaundice rarely result from heart disease but are common in gastro-intestinal disorders. The electrocardiogram is invaluable since it is generally abnormal in heart disease. The X-ray is usually more helpful in gastro-intestinal disease. The greatest difficulty arises when both kinds of disorders occur together. Unfortunately such a concurrence is common; then the keenest diagnostic acumen may be none too keen. This particular field is still a fertile one for further cultivation. The last word has not yet been said.

Hemorrhage From Gastritis---A Gastroscopic Study*

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THAT varying degrees of hemorrhage may occur from gastritis has long been recognized by a number of European authors. In this country, however, little attention had been paid to chronic gastritis until very recently, when interest was stimulated by the development of the flexible gastroscope (1). In the ten year period 1924-1933 a diagnosis of gastritis with hemorrhage was made in only five cases in the Massachusetts General Hospital. In the four year period 1933-1937, however, since the common use here of the flexible gastroscope (2), this diagnosis has been made in twenty cases. In other words we are now making a diagnosis of gastritis with hemorrhage ten times as frequently as formerly.

Among the earliest writers to consider gastric erosions as a cause of hemorrhage was Langerhans (3) (1891) who, in a case of eclampsia, reported severe bleeding from erosions in the stomach. Death was hastened by the bleeding, and autopsy showed catarrhal gastritis with hemorrhagic erosions. Nauwerck (4) (1897) noted small superficial hemorrhagic erosions in the stomach of a patient who died of a perforated gastric ulcer. Einhorn (5), Pariser (6) and Mintz (7) should also be mentioned among the early

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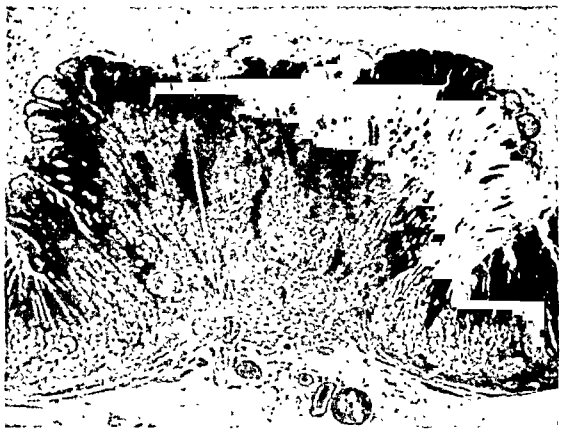


Fig. 1. Low power photomicrograph showing erosion typically located on crest of fold.

writers on this subject. Recent authors include Faber (8), Schindler (9), Moutier (10), Korbsch (11), Henning (12), Delore (13) and the present writer (14). Faber, in pointing out the clinical significance of chronic gastritis without ulcer, says, "The next symptom to discuss is hemorrhage, which from early days has been regarded as a sure sign of ulcer. But hemorrhage, even sometimes very severe, as fresh hematemesis or melena, also appears to be a very frequent symptom of these gastritis cases. Torben Anderson found hematemesis 5 times and melena 3 times among his 21 cases; 3 of Nicolaysen's 7 cases had a large hemorrhage, and 5 of Bj. Dahl's cases had hematemesis. Nearly all the cases had periodic occult hemorrhage. As all the cases exhibited advanced gastritis with erosions, it is not surprising that hemorrhage occurred. As already mentioned, Dieulafoy formerly observed even fatal hemorrhage after what he called *exulceratio simplex* in gastritis, in other words, after gastric erosions." Schindler, Ortmayer and Renshaw (9) likewise have discussed hemorrhage from gastritis and have pointed out that "gross, sometimes fatal, hemorrhages from gastritis have occurred." Korbsch (11) too has said, "It is certain that

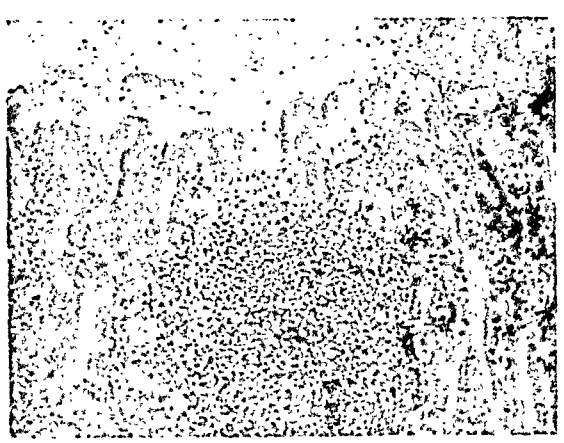


Fig. 2. High power photomicrograph of chronic gastritis showing slight erosion, fibrinoid necrosis, and marked lymphocytic infiltration.

gross bleeding can occur in chronic gastritis and that hematemesis is no longer to be considered a sure sign of ulcer." Henning (12) believes "that gross gastric bleeding in gastritis is not secondary in frequency to bleeding from tumors and ulcers." We thus have ample corroboration of our own experiences in hemorrhagic gastritis.

Hemorrhage from gastritis may be mild or severe. Any classification as to the degree of hemorrhage is necessarily somewhat arbitrary. In our twenty-five cases of gastritis with hemorrhage nine showed red counts below three million and were classed as severe hemorrhage. Three of these had red counts of 1.3 to 1.7 million, were almost moribund on admission, and required intravenous fluids and transfusions. One patient, with a history of very severe hematemesis following a large intake of bay rum and rubbing alcohol, died of hemorrhage from acute gastritis a few hours after admission to the hospital. Autopsy showed the only source of the bleeding to be multiple gastric erosions.

The signs and symptoms of chronic gastritis have



Fig. 3. Photomicrograph of gastric mucosa from patient with severe hemorrhage from chronic gastritis. Note erosion, fibrinoid necrosis, marked cellular infiltration, and lymph follicle formation.

been discussed in a previous paper (14). They are indefinite and inconstant. They may simulate peptic ulcer. In the twenty cases of acute and chronic gastritis confirmed by gastroscopy the age ranged from 30 to 60 years. There were 14 men and 6 women. There was a history of excessive use of alcohol in 5 cases, moderate intake in 5, rare or no intake in 10. Hematemesis occurred in 15 cases, and in most of these melena was also present; melena without hematemesis occurred in 5. Gastric analysis was done in 11 cases, and in 2 showed no free hydrochloric acid one-half hour after histamine. The other 9 cases showed 40 to 86 c.c. of N/10 NaOH one-half hour after histamine. Hence it appears that the degree of acidity is very variable. X-ray examination was done in all cases. A diagnosis of hypertrophic gastritis was made by X-ray four times, and confirmed by gastroscopy every time. A positive roentgen diagnosis of hypertrophic gastritis is significant, and is usually confirmed by gastroscopy. Negative X-ray findings are, however, quite common in hypertrophic gastritis.

The pathological picture in chronic gastritis shows

that bleeding takes place from an erosion in the mucous membrane. That such erosions commonly occur on the crests of the rugae is borne out gastroscopically and histologically. In Figure 1* the histological appearance of such an erosion is well illustrated. Note that the break in the epithelial lining is on the crest of the fold. Many of the mucous glands are darkly stained and contain no mucus. Hence the protective layer of mucus normally present is markedly diminished in and near the eroded area. Figure 2 is a high power photomicrograph showing chronic gastritis with marked lymphocytic infiltration of the mucosa, and a layer of fibrinoid necrosis covering a small erosion. These photomicrographs were taken from a stomach resected for duodenal ulcer. Figure 3, however, shows the histologic appearance of chronic gastritis not associated with ulcer or carcinoma. This patient had severe bleeding from gastritis alone. Because of tarry stools and a hungry feeling in the epigastrium he had had a gastroenterostomy performed at the age of sixteen at another hospital. Tarry stools continued intermittently, however, for thirteen years with severe hematemesis the day before admission to this hospital. Alcoholic history was negative. On entry the red count was 1.7 million, hemoglobin 40 per cent. One month later, after medical management and transfusion, hypertrophic gastritis was demonstrated by X-ray and gastroscopic examination. Because of the hemorrhage resection of the pylorus and duodenum was done, but failed to disclose the source of the bleeding. Pathological examination of the resected specimen showed no gross lesion present on either the gastric or duodenal surfaces. Microscopic examination (Fig. 3), however, confirmed the gastroscopic and X-ray diagnosis of chronic gastritis. Note the loss of epithelial surface, marked cellular infiltration and lymph follicle formation.



Fig. 4. Case 1. Gastroscopic appearance of erosion on crest of fold. Mild bleeding from hypertrophic gastritis.

The appearance of the mucosa as seen through the gastroscope is variable, depending on the degree of the hemorrhage and the time interval after the bleeding. Sometimes in the mild cases there is only a superficial gastritis with mottled areas of edema and reddening. Usually, however, there is more definite evidence of a long-standing chronic gastritis with a verrucous appearance of the mucosa and reddening of the crests of the rugae, sometimes with marked edema. Small erosions or shallow ulcerations may be demonstrable. If the examination is undertaken early, bright red blood may occasionally be seen lying in the dependent portion of the stomach, or trickling away from an inflammatory area or an erosion. Moutier (10) describes the gastroscopic appearance in hemorrhagic gastritis, and shows colored illustrations. He says all stages are seen from the simple congestive forms to the hemorrhagic lesions, in the latter cases the folds being generally large, swollen, and brightly colored, and sometimes spotted with whitish placques. Moutier feels that such an altered mucosa presents a special fragility, gastroscopy demonstrating a thin leakage of blood high up on the lesser curvature.

The treatment of gastritis includes rest in bed, intravenous fluids and transfusions for the severe cases, regulation of diet, dental attention, and elimination of alcohol and tobacco for all cases. Undue mental strain should be avoided. Gastric lavage has not been found necessary.

The following are detailed reports of a few cases of gastritis with varying degrees of hemorrhage:

Case 1. J. McC., M. G. H. No. 17046. Female, 55, entered the hospital February 11, 1937, complaining of epigastric pain, hematemesis and melena of one and a half years' duration. Alcoholic history was negative. A year and a half ago following hematemesis and syncope she was admitted to another hospital, transfused, and a diagnosis of duodenal ulcer was made by X-ray. Tarry stools continued intermittently. There was considerable epigastric distress with some relief by feed. On admission to this hospital the red count was 5.5 million, hemoglobin 75 per cent. Gastric analysis showed normal acidity. X-rays of the esophagus, stomach, duodenum and colon were negative. Gastroscopy showed normal pylorus, normal peristalsis, antrum smooth, red, and glistening. The rugae in the body of the stomach were particularly red, edematous and tortuous, with an erosion (Fig. 4) on the crest of one fold on the greater curvature which was deep red in color and appeared like clotted blood. In the upper part on the posterior wall, the appearance was markedly verrucous with two saucer-shaped depressions about ½ to 1 cm. in

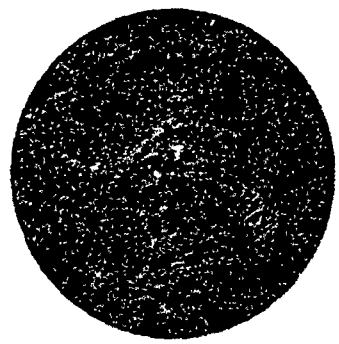


Fig. 5. Case 1. Showing verrucous appearance indicating hypertrophic gastritis.

*I wish to acknowledge with thanks the cooperation of Dr. Tracy B. Mallory and Dr. John I. Bradley in obtaining these photomicrographs (Figs. 1 and 2).



Fig. 6. Case 2. Small erosion of antrum in chronic gastritis with hemorrhage. Note raised collar of swollen mucosa with warty appearance, formed by heavy infiltration of inflammatory exudate and presence of connective tissue.

diameter (Fig. 5). Diagnosis by gastroscopy: hypertrophic gastritis with erosions. Definite improvement was obtained on a bland diet, but occasional tarry stools were observed.

Comment: Here we have a history of a moderate degree of melena of over a year's duration with conflicting X-ray reports regarding peptic ulcer. Very soon after a period of melena X-ray examinations by our own senior roentgenologists failed to show any ulcer or other abnormality of the gastro-intestinal tract. Gastroscopy, however, showed definite hypertrophic gastritis with erosions, apparently the only source of bleeding at the present admission.

Case 2. M. I. B., M. G. H. No. 329407. Female, 37, entered the hospital March 12, 1934, because of gas, sour eructations, nausea, vomiting, epigastric pain relieved by food or soda, and tarry stools. All symptoms had been intermittent for twelve years. Alcoholic history was negative. On admission the red count was 4.9 million, hemoglobin 80 per cent. Two stool examinations were negative for occult blood. Gastric analysis showed no free hydrochloric acid half an hour after histamine. X-ray examination showed no evidence of organic disease of the esophagus, stomach, or duodenum. Barium enema was negative except for diverticulosis, which, in view of her symptoms and the rarity of bleeding from diverticulosis, was regarded as an incidental finding. Gastroscopy showed pinpoint red erosions on the anterior wall of the antrum (Fig. 6) in an area which was granular in appearance and showed small elevations and depressions. On the greater curvature in the body of the stomach the rugae were abnormally prominent and showed clubbing with an erosion on the crest of one such fold (Fig. 7). The mucosa showed a verrucous appearance. Diagnosis by gastroscopy: hypertrophic gastritis with erosions. On a bland diet with mineral oil and belladonna there was improvement.

Comment: This case illustrates a mild degree of bleeding coming almost certainly from the upper gastro-intestinal tract. X-ray examination of this region was negative but gastroscopy showed hypertrophic gastritis with erosions.

Case 3. E. F. H., M. G. H. No. 350190. Male, 41, entered the hospital on December 10, 1935, complaining of heartburn, anorexia and nausea of one year's duration. For six months there had been an empty, gnawing feeling in the epigastrium about four hours after meals, relieved by food. Two months before entry he had passed a black stool and had vomited some material containing black specks. There had been a loss of about thirty pounds in weight. Alcoholic history was negative. Physical examination showed moderate pallor, red blood count 3,900,000, hemoglobin 70 per cent, smear normal. X-ray examination of the gastro-intestinal tract showed a low dilated stomach, containing a moderate amount of fluid. All the rugae were very markedly thickened. Duodenal cap appeared definitely normal. The findings were those of hypertrophic gastritis. Gastroscopic examination a few days later was reported as follows: "The gastroscope passed easily, the patient cooperated well, and the view was very good. The pylorus was well seen, and there was normal peristalsis passing over it. The rugae of the greater curvature were perhaps slightly thickened and did not entirely disappear on inflation. In the valleys between the folds were numerous very bright red streaks, indicating a superficial gastritis. On the posterior wall and lesser curvature there were numerous rounded hillocks and a somewhat verrucous appearance, indicating hypertrophic gastritis. There was no fresh bleeding and no erosion or ulceration could be demonstrated. The findings were those of superficial and hypertrophic gastritis." The patient was placed on a bland six-meal diet with ferrous sulphate and liver extract, and discharged improved. Six months later, after neglecting treatment, his symptoms had recurred.

Comment: In this case we have moderate hematemesis and melena, explained by X-ray and gastroscopic diagnosis of hypertrophic gastritis.

Case 4. M. W. G., M. G. H. No. 30520. Male, 53, first entered the Medical Out Patient Department in October, 1933, complaining of dull, gnawing epigastric pain of one

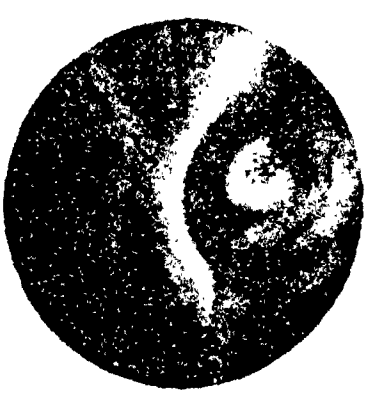


Fig. 7. Case 2. Erosion on crest of club-shaped fold in chronic hypertrophic gastritis with hemorrhage.

year's duration. X-ray examination at that time showed no evidence of organic disease of the esophagus, stomach, or duodenum. Improvement was noted on a six meal bland diet, to which, however, he adhered for only a few months.

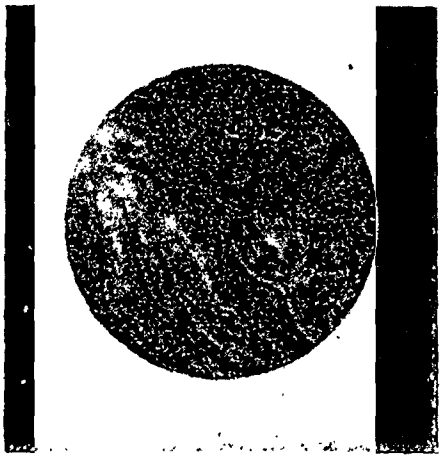


Fig. 8. Case 4. Marked inflammatory verrucous appearance of greater curvature and posterior wall in chronic alcoholic with moderate hematemesis. Chronic hypertrophic gastritis.

In March, 1937, he again entered the Medical Clinic because of intermittent recurrence of gnawing epigastric pain of five months' duration and vomiting of one pint of blood two weeks prior to entry. Alcoholic history showed heavy intake of whisky as a young man, none during prohibition, then heavy drinking again during the past four years. Two X-ray examinations of the upper gastrointestinal tract failed to show any organic disease that would account for the hematemesis. A diverticulum of the third portion of the duodenum was regarded as an incidental finding. Gastroscopy showed a normal antrum and pylorus, with normal peristalsis. The rugae were small and beaded and the mucosa reddened with an inflammatory verrucous appearance, particularly along the greater curvature and posterior wall (Fig. 8). The findings were those of hypertrophic gastritis. Improvement was noted on a six-meal bland diet with the elimination of alcohol and tobacco.

Comment: This history records a moderate degree of hematemesis, prolonged intake of alcohol, essentially negative X-ray findings on three examinations, but definite evidence of hypertrophic gastritis by gastroscopy.

Case 5. S. M.*, B. M. No. 32246. Male, 60, entered the hospital March 20, 1937, because of pallor and dizziness of three days' duration, hematemesis and melena of ten days' duration. There was a history of excessive alcoholic intake for many years, consisting of several daily drinks of whisky or gin. On admission physical examination disclosed extreme pallor and dehydration, with a blood pressure of 94 systolic, 35 diastolic. The red count was 1.5 million, hemoglobin 35 per cent. The patient was stuporous and in a very critical condition. After repeated transfusions, however, there was marked improvement. Two X-ray examinations about two weeks after admission showed the esophagus normal, the stomach unusually high in position and therefore hard to visualize. The duodenum was running posteriorly and was seen in profile only in the lateral view. No ulcer craters or filling defects were seen in the stomach, pyloric valve, or duodenum. Films of the small bowel taken at frequent intervals revealed no positive evidence of disease. Barium enema was negative. Gastroscopy was reported as follows: "The antral sphincter remained partially closed throughout the examination but a partial view was obtained into the antrum, which appeared normal. The rugae throughout the body and especially in the fundus of the stomach were not hypertrophied but were definitely beaded and reddened along their crests (Fig. 9), and in some places presented a slightly tortuous appearance. Some areas between the folds showed very marked inflammatory reddening and there was one small erosion on the crest of several converging rugae. This erosion was healing. It had a whitish base and appeared about 3 to 4 mm. in diameter and 2 mm. deep. In the acute stage of this gastritis a few weeks ago I believe profuse hemorrhage could have occurred. Much healing has undoubtedly taken place since the hemorrhage. The findings indicate a marked hypertrophic gastritis with erosions."

Comment: In this case we have massive hemorrhage from the upper gastro-intestinal tract, a long history of excessive use of alcohol, a critically ill patient who recovered by repeated transfusions, negative X-ray examinations, but gastroscopic evidence of hypertrophic gastritis with erosions.

CONCLUSIONS

Gastritis is a very important cause of bleeding from the stomach.

Varying degrees of hemorrhage from chronic superficial or hypertrophic gastritis may take place in the absence of other demonstrable pathology in the gastrointestinal tract.

Twenty cases of acute and chronic gastritis with hemorrhage have been studied by gastroscopy. The only likely and demonstrable source of bleeding in these cases was a superficial or hypertrophic gastritis, often with one or more erosions in the gastric mucosa.

As an etiological factor in massive bleeding from gastritis excessive use of alcohol is the most important.

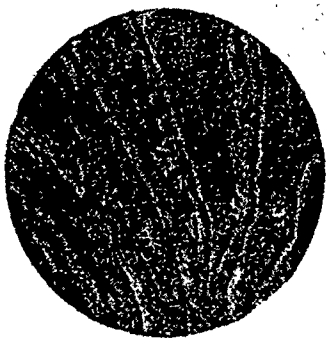


Fig. 9. Case 5. Beaded appearance of rugae and reddening of crests of rugae with erosions in chronic alcoholic with severe hematemesis and melena. Chronic hypertrophic gastritis.

*I should like to acknowledge the courtesy of Dr. William P. Thompson in granting permission to report this case.

For accurate diagnosis of gastritis gastroscopy is indispensable.

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DISCUSSION

DR. JULIUS FRIEDENWALD (Baltimore, Md.): Massive gastric hemorrhage is always alarming. Fortunately the incidence of this complication is not very frequent. Gastric hemorrhage occurred in 22 per cent of our ulcer cases. Of these, 38 per cent were single and 60 per cent were multiple. Of the 22 per cent in which hemorrhage occurred, but 14 per cent were massive in type. Among our cases melena was twice as frequent as gastric hemorrhage.

In our experience profuse hemorrhages occur most frequently in the latent periods of ulcer when the other symptoms have subsided or even when the ulcer has been considered healed. I am firmly convinced that blood pressure readings play a more important role in the prognosis of gastric hemorrhage than the low hemoglobin readings, which may even fall as low as 35, with subsequent recovery. A fall of blood pressure to from 80 to 85 systolic, without being followed by a rise, is always an alarming sign. The prognosis ordinarily to life in gastric hemorrhage is good. There were but three fatal instances in our series of one thousand ulcer cases.

Hemorrhage usually ceases under the usual medical management; however, there are recurrences of massive bleeding occasionally in spite of active treatment. In these, surgical intervention should be considered even in spite of the great danger entailed in such a procedure. With improved surgical preparation and technic, resection of the bleeding area may be undertaken with a hope of a satisfactory outcome.

The following case has recently been seen in consultation: A man of fifty-three years gave a definite history of ulcer extending over a period of two months. He was suddenly seized with successive massive hemorrhages which recurred notwithstanding most careful medical management including transfusions. His red blood cell count fell to 1,600,000, his hemoglobin to 30, and his blood pressure was 80. As there seemed no hope of preventing further recurrences, operation was undertaken. A large indurated cartilogenous-like ulcer, two and one-half centimeters in diameter, was discovered high up on the lesser curvature several centimeters from the esophagus. One margin of the ulcer was bleeding profusely and a large open-mouthed vessel was seen. The ulcer was resected. It was perfectly evident that the bleeding could not under any condition be checked from a vessel of this size by medical measures.

DR. HORACE W. SOPER (St. Louis, Mo.). Since my paper on the subject of hematemasis some six years ago, I have had more experience in the treatment of massive hemorrhage.

The expectant method of treatment is almost universally employed by physicians who see these patients. The blood is allowed to remain in the stomach. This incites vomiting the next day and the physician fears a recurrence of the hemorrhage. In brief, he is in the dark and does not know what is happening in the stomach.

In the method which I advocate, I term the "direct attack." A No. 16 Levin soft rubber catheter is passed into the stomach and the stomach lavaged by means of a large piston syringe. It is easy by this method to break up large blood clots without unduly disturbing the patient. When the stomach contents have been removed, continuous syphonage is instituted. I do not employ the suction apparatus but allow whatever secretion forms to pass out into a container by the side of the bed. If bright red blood continues to flow through the tube it means that the hemorrhage is arterial and immediate surgical operation is indicated. At all times the physician is in complete control of the situation.

Furthermore, keeping the stomach secretion free initiates early and rapid healing of the ulcer. The chlorides you remove are replaced intravenously. By the third day one is able to begin feeding egg albumin water and gelatine water, and usually by the end of the week the high calorie milk-egg mixture. During this feeding time, the tube remains in place, clamped off, but allowed to remain open from time to time to test the secretion with congo red paper.

The retention of the tube in the stomach does not incite gastric secretion nor contracture.

DR. PAUL M. ASCHNER (New York, N. Y.): Mr. President and Gentlemen: I believe it was about four or five years ago that I presented before this Association a study of some 120-odd specimens of resected stomachs in which subtotal resection had been done for various gastric lesions of the gastric group. We concluded from those studies, both clinical and pathological, that ulcer does not occur in a normal stomach; that ulcer is a stage in the disease of the gastric mucous membrane, and we have had illustrated here very beautifully today, with the gastroscopic method of examination, the type of lesions which we found pathologically in our resected specimens.

From this type of patient we have two distinct groups of cases. We have the type of case in which there is extensive microscopic erosion of the duodenous mucous membrane with or without a co-existent actual macroscopic ulcer. These cases are not infrequent and can bleed very profusely and fatally.

These types of lesions are likely to occur in the younger individuals. The older patients who have had ulcer disease over a great period of years and arrive at the age of fifty or over with their ulcer waxing and waning are likely to have a calloused type of ulcer of the duodenum, or the stomach which erodes gradually into one of the large vessels. This type of patient has an enormous hemorrhage which usually, as has been mentioned, requires surgical intervention. The first type of erosion may respond to the medical treatment which one of our discussers has just described.

In regard to symptomatology in these patients, there is another factor that enters and that is the factor of sensitivity to pain, which has been reviewed for many years by Dr. Libman and dilated upon by Dr. Crohn, which is a valuable point to bear in mind. While it is true most

patients with ulcer disease have a neurotic constitution, neurosis and sensitivity to pain do not go parallel. You may have patients who are insensitive to pain and whose lesions go on developing to a marked extent with very little symptomatology and these are the patients that get so-called unexpected perforations and hemorrhage.

DR. LEMUEL C. McGEE (Elkins, W. Va.): Mr. President, inasmuch as the acute massive hemorrhage is a medical problem for the most part, rather than a surgical one, we still have, after the patient has recovered from the immediate hemorrhage, the question of what shall be the future management. There are very few objective criteria to help one decide the proper procedure.

The young individual's prognosis is good if he will follow advice, and for that reason I suspect a large number of us do not advise resection after the first hemorrhage in the younger group of patients. In the group past fifty years of age we see the mortality has increased to such an extent that it becomes advisable to resect the ulcer soon after checking the first massive hemorrhage. After the patient has been made suitable for major surgical procedures the importance of this course is emphasized by the pathological specimen presented here and the discussion by Dr. Friedenwald. Since the mortality of the older group is as much as 10 per cent, as mentioned by Dr. Blackford, we may assume that the condition of the arterial wall is the important factor. If we could have some way of determining the condition of the arterial wall directly by the gastroscope or by the condition of arteries externally, it would be a great help to us.

I should like to ask Dr. Blackford if he has attempted any correlations between objective measurements, such as the degree of sclerosis of the retinal arteries, and the occurrence of repeated hemorrhage in ulcer patients of various ages.

DR. ALBERT F. R. ANDRESEN (Brooklyn, N. Y.): Both speakers have shown the reason why, in general, medical treatment for massive gastric hemorrhage is safer than surgical. Our experience, in patients who have been subjected to operation on account of persistent hemorrhage or who have died and have had a necropsy performed, has shown that the bleeding either came from multiple erosions over large areas, as demonstrated by Dr. Benedict, or from deep ulcers, involving large vessels and held open by large, tough, horny masses of induration, as described by Dr. Friedenwald. The large bleeding areas are obviously not amenable to surgical care, and the horny masses are friable, almost impossible to suture and not safe to excise in a patient suffering from the effects of hemorrhage.

The indications in gastric hemorrhage are simple: 1. Shock should be treated by rest, by morphine and by maintaining body heat, especially by the avoidance of ice internally or externally. 2. Complete rest, in bed, with physiologic rest of the stomach by means of frequent small feedings, preferably containing gelatin, to avoid violent and possibly dangerous hunger contractions. 3. The protective effect of the low blood pressure, preventing dislodgement of the thrombus which stops the hemorrhage, must be encouraged by avoiding sudden increases in blood volume or pressure. This involves the avoidance of stimulants and of intravenous or subcutaneous injection of fluids. Even transfusion may often cause a recurrence of active bleeding and should be avoided except in cases of actual air hunger, when usually 150 or 200 c.c. of blood will be sufficient. Blood regeneration is usually very rapid after cessation of bleeding.

DR. WILLIAM A. SWALM (Philadelphia, Pa.): I believe that this presentation brings out the fact that gastritis of the erosive type is a definite entity and that many hemorrhages occur in cases that are not of the true, peptic ulcer type. The Europeans have told us that the superficial musculature beneath the glandularis structure is the dividing line between ulcerative gastritis and peptic ulcer. May in collaboration with Müller has noted in pathological studies that if he finds hemorrhagic infarct, deep into the glandularis, rather than on the superficial muscularis mucosa, hemorrhage is likely to occur, and I think that is an important observation.

I think another important observation is that Christensen found gastroduodenitis in a great many of his so-called peptic ulcer cases. They had duodenal defects and, on operation they found gastroduodenitis and not true peptic ulcer.

DR. DANIEL N. SILVERMAN (New Orleans, La.): I should like to make mention of our recent experience in the treatment of persistent hemorrhage not alone from peptic ulcer, but also from severe cases of chronic ulcerative colitis and dysentery, and that is following the method recently devised by Marriott, of London, who showed single transfusions 500 c.c. of blood, which were instrumental in elevating the hemoglobin only 5 to 10 per cent, while with his method of continuous transfusion he had been able to elevate it much beyond the single transfusion, and keep that elevation, and had given as much as 3000 to 5000 c.c. of this citrated blood mixture within a short period of forty-eight hours.

In our experience, of course, which was with just a few cases, whereas Marriott is ready to publish some five hundred cases so treated, we were able to get results in these few cases in which previously repeated massive transfusions were given daily in the amounts of some 500 c.c. of blood without improvement.

We do know that in other diseases than peptic ulcer, hemorrhage is sometimes death dealing and single transfusions have not been as beneficial in those few cases previously mentioned as the so-called continuous drip blood transfusion of Marriott.

DR. MAX EINHORN (New York, N .Y.): I think this is a matter of clinical importance and I congratulate the two gentlemen, Dr. Blackford and Dr. Benedict upon their important papers.

I wish to make only a few remarks with regard to treatment. First, what is called hypertrophic gastritis is not always a real gastritis but hypertrophy of the mucous membrane, which is a secondary condition due to hyperacidity which results in hypertrophy of the glands.

With regard to erosions, which I described many years ago, they usually do not give rise to very much hemorrhage. We find in these cases small pieces of mucous membrane in the wash water—fasting condition, as a constant phenomenon. They have to be treated and can be treated very effectively by nitrate of silver spray—not washing but really spraying the stomach. Besides this galvanic current given intragastrically is also beneficial. I have had very good results with the above two means of treatment.

Very rarely it happens that an erosion can lead to a massive hemorrhage. That is the type described by Dieulafois as very important and in such cases an operation may be necessary.

In regard to the treatment of massive hemorrhage, I would like to say that the principle of rest is of the greatest importance, no matter what you do. Many years ago I introduced during the hemorrhage, or an hour or two later, the duodenal tube, and could see by aspirating very gently whether there was blood, and then let the tube go further, and, if it is in the duodenum, start with nutrition, giving them milk.

I do not speak now of a few cases, but I will mention my experience, which covers a very big field. In the severe cases I would say we can have good results—simply the rest treatment. The ice bag I am in favor of, then adrenalin, opiates when necessary, and thromboplastin we can

give, but I don't think that is the main thing, but resting of the stomach and keeping the patient quiet, no visitors, no talking, an ice bag, a little bit of water by mouth, and the rest by the duodenal tube.

DR. RUDOLF SCHINDLER (Chicago, Ill.): Mr. President and Members of the Association: This table (Table I) gives a classification of the gastric hemorrhagic phenomena other than those of ulcer, syphilis and tumors.

TABLE I

Classification of the gastric hemorrhagic phenomena other than those of ulcer, syphilis and tumors

I. MUCOSAL HEMORRHAGES	II. GROSS HEMORRHAGES
A. in the normal not inflamed gastric mucosa	A. Profuse parenchymatous bleeding in chronic hypertrophic gastritis (only one observation)
1. without other organic disease (often combined with pigment spots or *hemorrhagic erosions*)	B. caused by ulceration having eroded a blood vessel
2. in ulcer-bearing stomachs	1. without inflammation (hemorrhagic erosion)
3. in all kinds of general hemorrhagic diatheses	2. in chronic nonspecific ulcerative gastritis
B. in the inflamed gastric mucosa	a. in chr. superficial ulcerative gastitis
1. in acute gastritis	b. in chr. hypertrophic ulcerative gastritis (most common form)
2. in chronic nonspecific gastritis	
a. in chr. superficial g.	
b. in chr. atrophic g.	
c. in chr. hypertrophic g.	

It is, in my opinion, to the great merit of Dr. Benedict that he has directed our attention to a phenomenon which is well known but rarely sufficiently appreciated; namely, the fact that gross and even fatal gastric hemorrhages occur, the origin of which is not ulcer or carcinoma. What is the cause of these hemorrhages?

We usually subdivide chronic gastritis into three groups, two of them having a certain relationship to each other; namely, chronic superficial and chronic atrophic gastritis, while the third form, the chronic hypertrophic gastritis is a different entity. Most of the profuse hemorrhages in gastritis occur in the chronic hypertrophic form from an ulceration eroding a small blood vessel; the same occurs, but very rarely, in the superficial form.

To call a gastritis a hemorrhagic gastritis because an erosion of a blood vessel causes gross hemorrhage, does not agree with the generally accepted definition of a hemorrhagic inflammation. In a hemorrhagic inflammation, the inflammatory exudate contains more or less red blood cells; the hemorrhage is part of the inflammatory process.

Such mucosal hemorrhages in gastritis are frequent. I have described and pictured them in 1922. They are found in all forms. Some occult blood may be present in the stools; however, until a short time ago I believed that these true inflammatory mucosal hemorrhages never would lead to gross gastric hemorrhage, but a few months ago I observed a case at Cook County Hospital, Chicago, which seemed to me to prove the contrary. A white man, thirty-eight years of age, had several times had severe attacks of vomiting of blood and wished to be operated on. When I emptied the stomach with an Ewald tube, thin, light-red blood came out of the tube. Gastroscopically almost the whole stomach showed the most severe hypertrophic gastritis, velvety swelling, formation of nodules and verrucae. No ulceration was seen, but blood was oozing constantly from the inflamed, swollen area into the cavity of the stomach. This was a parenchymatous bleeding, a true chronic hypertrophic hemorrhagic inflammation causing gross hemorrhage.

It is evident that the described gross hemorrhages coming from ulcerations with eroded blood vessels do not belong to this group. They may be called chronic hypertrophic (or superficial) ulcerative gastritis, causing gross hemorrhage.

The fact that there are gross hemorrhages without ulcer, carcinoma, and so forth, but also without inflammation, is almost always forgotten. I am referring to profuse hemorrhages caused by non-inflammatory hemorrhagic erosions (1). They are rare. I have observed only three cases.

The following is characteristic: A white woman, fifty-six years of age, had had several gross hemorrhages. X-ray examination with the compression technic did not reveal any evidence of gastric disease. The gastroscopic impressions were:

(1) Numerous mucosal hemorrhages without inflammation;
(2) Multiple pigment spots; and
(3) Two *hemorrhagic erosions.*

Two days later the patient had again a severe but not fatal gross hemorrhage.

The knowledge that profuse gross hemorrhage occurs frequently from other conditions than ulcer and carcinoma must decisively influence our therapeusis.

DR. EDWARD B. BENEDICT (Boston, Mass.): I want to thank Dr. Schindler, Dr. Einhorn, Dr. Swalm, Dr. Andresen and Dr. Aschner for discussing the paper. It seems to me that a classification of chronic gastritis with hemorrhage is difficult. I called my paper "Hemorrhagic Gastritis," but in the publication I shall call it "Hemorrhage from Gastritis," because I think hemorrhage may occur in chronic superficial or chronic hypertrophic gastritis. I am trying to use Dr. Schindler's classification. I have not seen hemorrhage in atrophic gastritis, although I believe it may occur.

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Cine-Fluorographic Studies of Lesions of the Gastro-Intestinal Tract*

By

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and

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CINE-FLUOROGRAPHY, as the name indicates, is the making of a motion picture record of the image seen on the fluoroscopic screen. Attempts to accomplish this purpose were begun by McIntyre (1) in Glasgow soon after the discovery of the roentgen ray. These efforts met with little success, however, when applied to the living patient. In this country, the late Dr. Eugene W. Caldwell conducted a series of such experiments beginning about 1906 and continuing for about fifteen years without any published success. Gastric motor phenomena were demonstrated more than twenty-five years ago by a motion picture film made from serial radiographs. In 1909, Kaestle, Rieder and Rosenthal (2) made thirteen successive radiographs of the stomach in twenty-two seconds. These were reproduced on a motion picture film, which, when projected, showed the passage of a peristaltic wave toward the pylorus. In 1910, Cole (3) demonstrated a method of making serial roentgenograms on a machine of his own design which employed a continuous X-ray film eight inches wide; he exposed areas of this film at regular intervals. Then, by a process of reduction and selection, combined with animation he was able to manufacture a film as a cinematogram. From 1921 to 1925, Reynolds (4, 5) of London, made extensive experiments leading at last to a successful motion picture of the fluoroscopic image of a thorax and various joints of the human body. More recently, Reynolds in England, Belot in Paris and Janker in Germany, employing greatly improved apparatus have successively made motion pictures of the fluoroscopic image.

REQUIREMENTS OF THE PROBLEM

The recording of a motion picture film of the movements of organs and joints of the living human being, is attended with considerable physical and mechanical difficulty. Any method which can be regarded as a solution of the problem must provide a technic which is safe, simple, convenient and inexpensive. Two methods may be suggested, namely, the direct and the indirect.

The direct method is the repeated exposure of any part of the human body to the X-ray beam recorded on a moving continuous X-ray film, as in the usual technic of making separate simple roentgenograms. This method is beset with many difficulties, is expensive and impracticable for routine examinations.

The indirect method makes a motion picture record of the fluoroscopic image. This method is obviously simpler, more accurate and less expensive.

DIFFICULTIES AND LIMITATIONS

Aside from the inherent mechanical difficulties this method is restricted by definite physical limitations. In solving the problem, which, after all, is that of focusing the greatest amount of light on the most highly sensitive photographic film, the following factors govern the result:

(1) The amount of energy in the incident X-ray beam. This is limited by the capacity of the X-ray tube and by the tolerance of the patient's skin.

(2) The light producing power of the fluoroscopic screen. This varies qualitatively and quantitatively according to:

(a) The chemical composition of the screen.

(b) The color of the fluorescence produced by the screen.

(3) The light-gathering power of the camera lens system.

(4) The photographic sensitivity of the film as related to the fluorescence of the screen.

As the limits of each of the above factors are widened, the greater is the scope of the method and the greater is the chance of success.

X-ray Tube: The X-ray tube we have found most satisfactory for this purpose is the G.E. 10 R.W. This tube can be safely operated at 100 KV with a current of 110 milliamperes for five seconds.

Skin Tolerance: When this tube is operated at 100 kilovolts, 110 milliamperes, at 40 cm. target-skin distance, with 1 mm. of aluminum and 5 mm. of wood filter, the estimated dose of radiation reaching the patient's skin is 500 roentgens per minute. This would be sufficient to produce an erythema in 48 seconds. The average time for each simple exposure has been five seconds which is repeated two or three times in each case. There is a rest period for the tube of 15 seconds between each five second exposure. This is well within the limits of safety. It is, therefore, apparent that the capacity of the X-ray tube is much more a limiting factor than is the tolerance of the patient's skin. If it were necessary, however, a further reduction in the amount of exposure of the patient could be brought about by synchronizing the excitation of the X-ray tube with the camera shutter so that the X-rays strike the patient only during those instants when the camera shutter is open. Although this is the arrangement employed by Reynolds we have not found it necessary because in five seconds a complete cycle of any moving organ of the body except the stomach can be recorded.

Fluoroscopic Screen and Photographic Film: The brilliance of the fluoroscopic image varies with the chemical composition of the screen while the photographic results depend upon the sensitivity of the film to that particular wave-length of light emitted by the screen. After many experiments made with all types

*Read at the Annual Meeting of the American Gastro-enterological Association, Atlantic City, June 7 and 8, 1937.

of available screens and photographic film we have found that the most desirable combination is a special screen emitting a yellow green fluorescence used in combination with Eastman Super X Film. This screen is made from a preparation of zinc sulphide developed by Dr. Leonard Levy and Mr. Donald West of London, Engand. It compares with a type B Paterson Screen.

Lens System: The lens employed is a Zeiss R-Biotar, with an aperture of 0.85 and a focal length of 5.5 cm. In order to cover the fluoroscopic field of 30 x 50 cm. it was necessary to place the lens at a distance of seven feet from the screen. This lens is fitted with a focusing mount and because it is used wide open no diaphragm is employed.

Camera: The Bell & Howell Filmo 70-D, 16 mm. camera, fitted with a special finder has been found to be most satisfactory.

Technic: Employing the above mentioned factors and the normal camera speed of 16 frames per second 80 pictures could be obtained in the exposure time of five seconds. This is sufficient to record the motions of such rapidly moving organs as the heart, lungs and diaphragm as well as to demonstrate the mechanism of swallowing. Films made of the esophagus require at least 12 frames to the second or a total of 60 frames to each exposure. If the camera speed is reduced to 8 frames per second the exposure time per picture is doubled and the apparent motion of the organs is proportionately increased to twice the normal speed.

In suitably thin patients the camera speed may be increased to 24 pictures per second, so that when the film is projected the apparent motion is slowed down proportionately, and permits more careful study and analysis of the film. Within narrow limits the speed of the apparent motion may be further diminished by reducing the rate of projection. Beyond this point, however, further slowing of the projection speed produces a flickering image.

CINE-FLUOROGRAPHY OF THE GASTRO-INTESTINAL TRACT

The investigation of the organs below the diaphragm is attended with considerable difficulty. This portion of the body is so opaque that the fluoroscopic image is much fainter than that seen in the examination of the chest. Since the total continuous time of exposure cannot be extended beyond a maximum of five seconds with the tube which we are using, the only way to increase the exposure per picture is to diminish the distance between the screen and the film and to reduce the camera speed to 8 frames or less per second. At this rate a clear picture can be obtained in a suitably thin patient. The time required for a normal peristaltic wave to pass downward along the full extent of the stomach has been estimated as averaging forty seconds. For that reason even a five second exposure is limited in its recording of movement.

In our efforts to obtain a film of the gastro-intestinal tract below the diaphragm we have shortened the screen-lens distance to five or even to 3.9 feet and reduced the camera speed to 4 to 8 frames per second. This has increased the amount of light which reaches the film from any unit area of the screen. With the shorter screen-lens distance the size of the field has necessarily been proportionately reduced so that only a part of the screen image can be photographed. It is therefore necessary to focus the camera accurately on the pathologic lesion.

With the equipment and technic described above, we have been able to obtain excellent films of the functioning in health and disease of the esophagus, stomach, duodenum and gall bladder, although the phase of gastric activity revealed by the film is so short that only a little of the real physiological activity of the stomach or duodenum can be demonstrated. Films of the act of swallowing show the manipulation of the opaque bolus in the pharynx and its peristaltic descent through the esophagus. The entire action is contained on a strip of film containing 40 to 60 frames, the projection of which would provide visible action for only a few seconds. By repeatedly printing this short film on a roll of film twenty-five to fifty feet in length the cycles of action may be projected over and over again for many minutes. This provides ample time for study of the physiologic action of the organs under investigation. Having obtained a good film it is necessary to have a projectoscope which will give the maximum amount of light and one in which the speed of the shutter can be cut down to a minimum without a flickering of the image. A Bell & Howell 1000 watt machine has proven to be most satisfactory.

FIELD FOR FURTHER IMPROVEMENT

At its present stage of development, the greatest needs in the field of cine-fluorography are:

(1) A method of prolonging the exposure so that a record of twenty to thirty seconds of action may be made at one time.

(2) A more brilliant fluoroscopic screen.

(3) X-ray tubes of greater capacity for longer periods.

(4) More sensitive films.

(5) Better correspondence between the sensitivity of the film and the light production of the screen.

Improvements in screen, X-ray films and tubes must await dvelopments by the chemists and physicists. Until they are available we must learn to make the best possible use of the remarkable materials and equipment which they have already placed in our hands.

ADVANTAGES OF CINE-FLUOROGRAPHY

By means of cine-fluorography a permanent record may be made of the functioning organs and parts such as the esophagus, diaphragm, stomach and duodenum, intestines and gall bladder, both normal and pathological. This motion picture record can be studied at leisure without danger of excessive exposure to the patient or examiner. It provides a means of comparing the state of the functioning organs or parts with previous motion picture records, thus demonstrating the results of operative, X-ray, radium or other therapy or the progress or recession of the disease. It furnishes, also, a means for building up a library of excellent teaching material. These motion picture films can be shipped to distant places for consultation and opinion on the condition of the patient at the present time or at any time in his previous history as represented on the films.

The method is simple, convenient, safe and relatively inexpensive. With further experimentation and improvement its scope doubtless will be broad-

ened, and it is probably destined to become an important division of roentgenological study.

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DISCUSSION

DR. CHESTER M. JONES (Boston, Mass.): I should like to make one comment. If ever I saw an excellent demonstration of aerophagia and "gas in the stomach," it has been shown here. I think this film could well be used for teaching purposes.

DR. A. C. IVY (Chicago, Ill.): I should like to congratulate Dr. Stetten and Dr. Stewart on the wonderful demonstration they have made. Those of us who are physiologists and have worked in the laboratory on animals have frequently prayed for an apparatus of this kind. For example, we have seen reversed waves on the esophagus with the fluoroscope and with the esophagus exposed through an opening in the chest. We have never been able to demonstrate them the way this film does. Never have we had available such a beautiful way of demonstrating how evacuation of the duodenal cap occurs.

It would be very interesting to extend such a study as this to the evacuation of the distal ileum, and also to the colon.

In conclusion, I hope that Dr. Stewart will be able to make copies of this film available to teachers of medical students at a cost that is not prohibitive.

DR. JOHN L. KANTOR (New York, N. Y.): We might add a vote of thanks to Dr. Einhorn, who has shown such a wonderful way of perpetuating his investigations from the earliest years of our specialty right up to the threshold of the future, as it were.

PRESIDENT JONES: That is a very justifiable remark.

DR. MAX EINHORN (New York, N. Y.): Mr. President, I wish to congratulate Dr. Stewart and Dr. Stetten on their very important work. There is a saying "Seeing is believing," and I think this demonstration helps a great deal to clarify the particular situation and that is the reason I am interested in it. I should like the two gentlemen to follow it up further, down the whole intestinal tract.

The Interdependence of Gastric Secretion and the CO_2 Content of the Blood and its Significance in the Alkali Treatment of Peptic Ulcer*

By

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THE usefulness of alkalis in the treatment of duodenal ulcer has been fully established by the fact that Sippy powders and other forms of alkalis are still in use many years after they were first introduced. Some clinicians attempt to achieve complete neutralization of the gastric contents while others are content to use alkalis only in sufficient quantities to control pain.

The hypersecretion of hydrochloric acid and the activity of peptic ulcer are so closely associated clinically that regardless of whether one or the other is the primary factor, effective neutralization of the gastric juice is a rational procedure which has yielded good results in many cases. While an ulcer may be so mild that comparatively little alkali is necessary to control symptoms and promote healing, patients with severe active lesions tend to produce such large quantities of acid that only heroic doses of alkali are effectual. Nevertheless, it is common experience that the patient with the most active ulcer, the most severe symptoms and the highest acid is the one who shows the least tolerance to alkalis, so that frequently, in the case with the greatest need for neutralization, the use of alkalis is limited by the increased tendency to alkalosis. Under these circumstances, a therapeutic dilemma develops, the explanation of which involves physiologic as well as pathologic considerations.

A tendency to alkalosis has been shown to be indicative of a severe ulcer. Jordan and Kiefer (1) have presented statistical evidence that intolerance to alkali therapy is an unfavorable prognostic sign in the medical management of ulcer. Additional observations include the fact that patients who are quickly upset by alkalis during the active phases of their ulcer, can often take the same dosage after the hypersecretory phase has passed without unduly raising the blood CO_2. These clinical observations suggest that the occurrence of alkalosis may be largely dependent upon the secretory activity of the gastric glands and associated changes in the electrolyte balance in the blood and body fluids.

Previous reports (Wilkinson (2), Hardt (3), Ellis (4), Gatewood (5)), have cited impaired renal function as a major etiologic factor. This is undoubtedly true in many cases, but it does not explain either alkalosis occurring in patients without evidence of kidney disease or the increase in tolerance to alkalis observed in some cases when there is no evidence of improvement in the condition of the kidneys. There is apparently some additional mechanism which determines the amount of load thrown upon renal tissue, which is the chief regulatory organ governing the acid-base balance of the blood.

*From the Department of Gastro-Enterology, Lahey Clinic, Boston.
Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, June 7 and 8, 1937.

Sodium bicarbonate, which is the most important antacid used in alkali therapy from the standpoint of the production of alkalosis, is a soluble salt readily absorbed from the gastro-intestinal tract and readily secreted unchanged by the kidney. Investigations (Kast (6), Jordan (7), Gatewood (5)) of the blood in the alkalosis state have disclosed an appreciable rise in the plasma pH, a marked rise in the CO_2 content and a decrease of the chlorides of the plasma. If the mechanism responsible for these changes, particularly the elevation of CO_2, is an accumulation in the blood of sodium bicarbonate absorbed as such and present because of delayed excretion by the kidneys, blood analysis should show an increase in sodium as well as bicarbonate. Actual measurements of the total base reported in this paper show that alkalosis may be present without an accumulation of base in the plasma.

When the total base, chlorides and CO_2 content are known, it is possible to construct a diagram of the electrolytes of the blood expressed in comparable units, i.e. mille-equivalents per liter (Figure 1). The total height of the column is determined by measuring the total fixed base which tends to remain constant at about 160 mille-equivalents per liter. The total anions are represented by a column of equal height. The bicarbonates and the chlorides are measured separately and the remainder which consists of protein, organic acids, sulphates and phosphates, is obtained by subtracting the sum of the CO_2 and the chlorides from the total base. In the normal, the bicarbonate is equivalent to about 30 mille-equivalents per liter, the chlorides to about 101 and the undetermined radicals account for about 29 mille-equivalents per liter. See Subject 1 (Figure 1).

Subject 2 (Figure 1) was a case of alkalosis with typical symptoms except there was no vomiting. The pH was elevated and the plasma bicarbonate was increased with almost identical lowering of the chlorides. The total base remained constant, showing that alkalosis can occur without an appreciable accumulation of base in the blood.

A reduction of the chlorides was found to be a regular concomitant of an elevated CO_2 content so

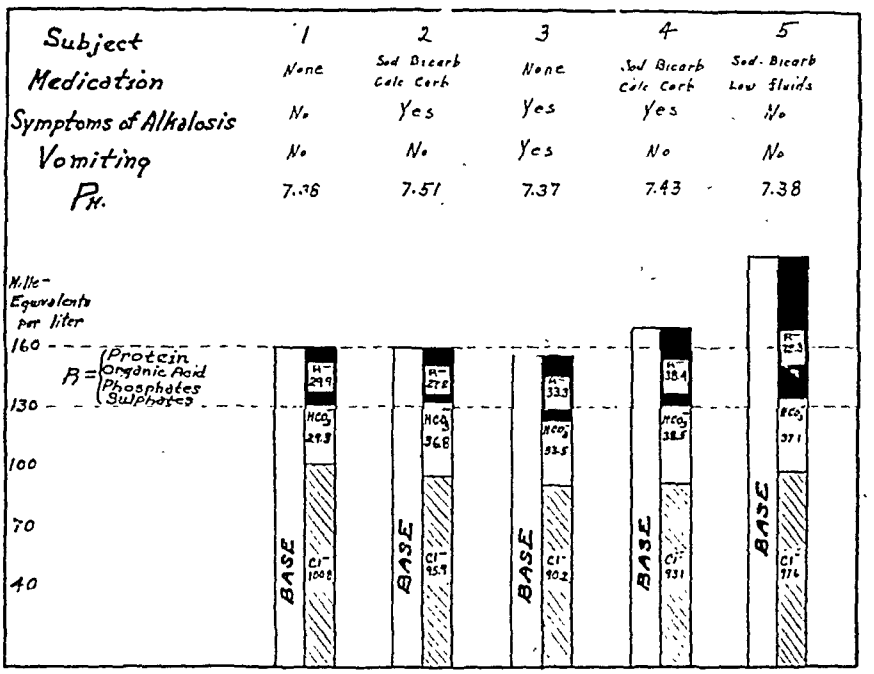


Fig. 1

that in every condition studied, an increase in the bicarbonate ion resulted in the displacement of an equivalent amount of chloride ion. It is to be noted that regardless of the changes demonstrated by the diagrams in Figure 1, the sum total of chloride and bicarbonate remains remarkably constant. The role of the chlorides, therefore, appears to be an important one.

The relationship of gastric secretion may be represented schematically by Figure 2. During gastric secretion, particularly during the stages of hypersecretion associated with ulcer, the parietal cells are actively engaged in manufacturing large quantities of hydrochloric acid which is a strong, highly dissociated acid. Under ordinary circumstances the acid is neutralized by food, products of digestion and the alkaline secretions present in the intestine. The chloride is reabsorbed to adjust the slight temporary relative increase in base, known as the alkaline tide.

If an excess of sodium bicarbonate is introduced into the stomach, neutralization of hydrochloric acid takes place and the chlorides pass into the intestine as sodium chloride. Here they are reabsorbed as in normal conditions with the exception that they carry into the blood sodium ion, which instead of coming from the blood by way of liver and pancreatic secretions, originates outside the body. The chloride ion therefore makes the circuit of being passed out of the

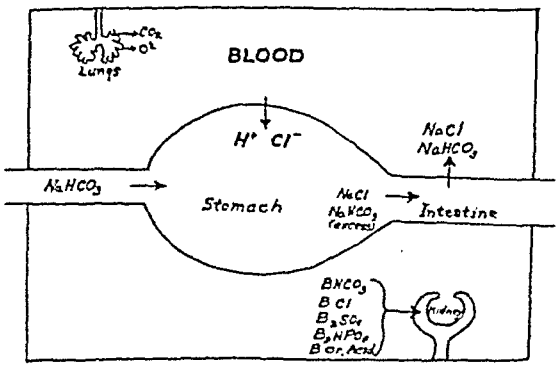


Fig. 2

blood into the intestinal tract and back into the blood, but the net result is that sodium is quantitatively added to the body. Further gain in sodium takes place as the excess sodium bicarbonate is absorbed as such, but this portion carries with it an acid radical (HCO_3) which also originates outside the body and permits the kidney to excrete sodium bicarbonate in the urine. Since it is necessary to conserve the chlorides. The real problem for the body is to find acid radicals to combine for excretion with the sodium ion which was absorbed as sodium chloride. Sodium appears in the urine combined with sulphates, phosphates, carbonates and organic acids, but in addition considerable chloride is lost. To compensate for the chloride depletion, the bicarbonate concentration of the plasma increases, resulting in a rise also in the free CO_2, which is part of the buffer system which prevents more than minimum changes in blood pH. This concept is offered as an explanation of the mechanism by which the blood CO_2 is elevated and the clinical observation that alkalosis occurs more readily when gastric hypersecretion is present because the quantity of sodium absorbed without the introduction of an equivalent acid radical is dependent upon the amount of hydrochloric acid neutralized in the stomach.

In a case of alkalosis caused by vomiting, as in Subject 3, Figure 1, there is some loss of base, but a much larger depletion of chlorides which operates in the same way to produce a relative increase in the combined CO_2 of the blood. This explains the clinical observation that patients with vomiting show the least tolerance for alkalis.

Dehydration is a prominent feature of alkalosis and tends to occur when there is a large excretion of sodium, since this element cannot be excreted without the loss of water. Subject 4, Figure 1, represents the changes in the blood when the water balance is upset in the presence of alkalosis. There is a definite increase in total base but the increase in the acid radicals occurs in the undetermined portion which consists largely of protein and organic acids. Subject

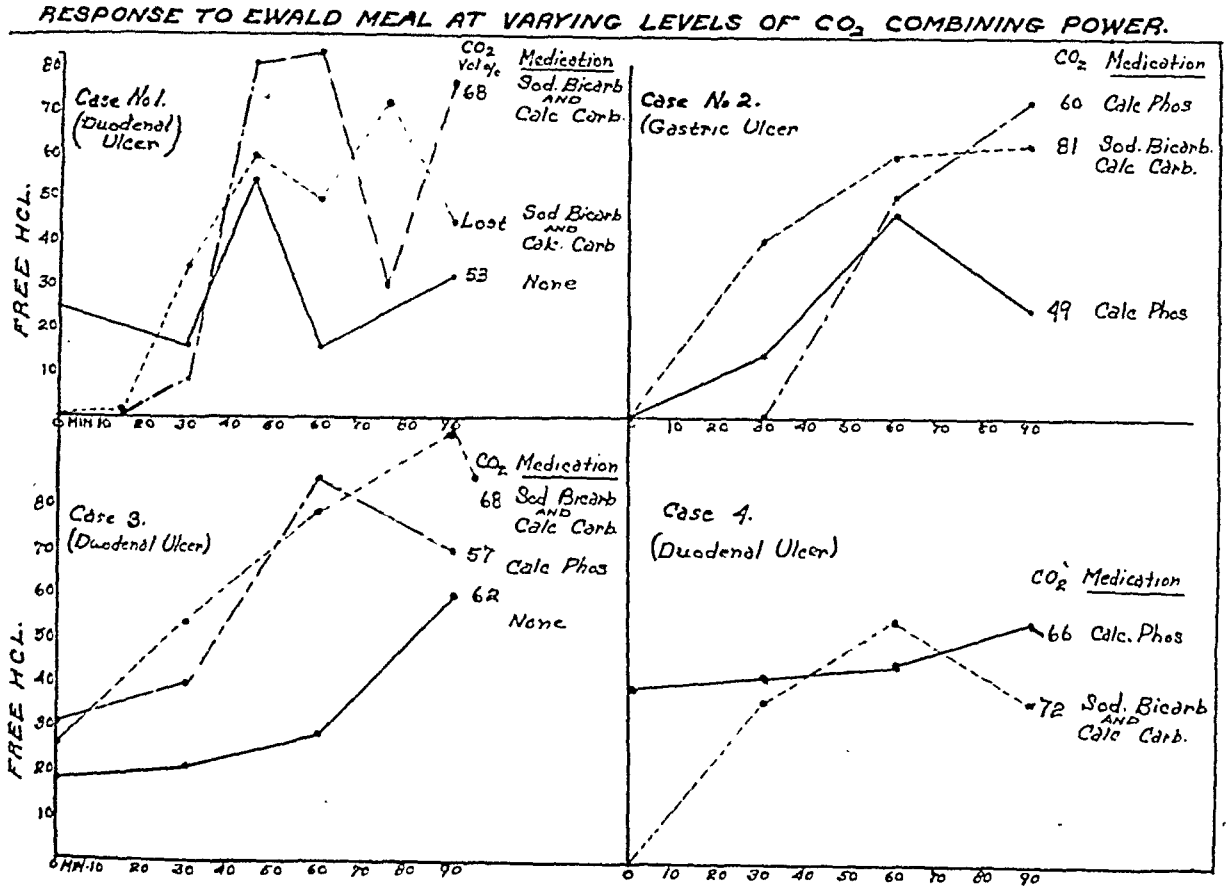


Fig. 3

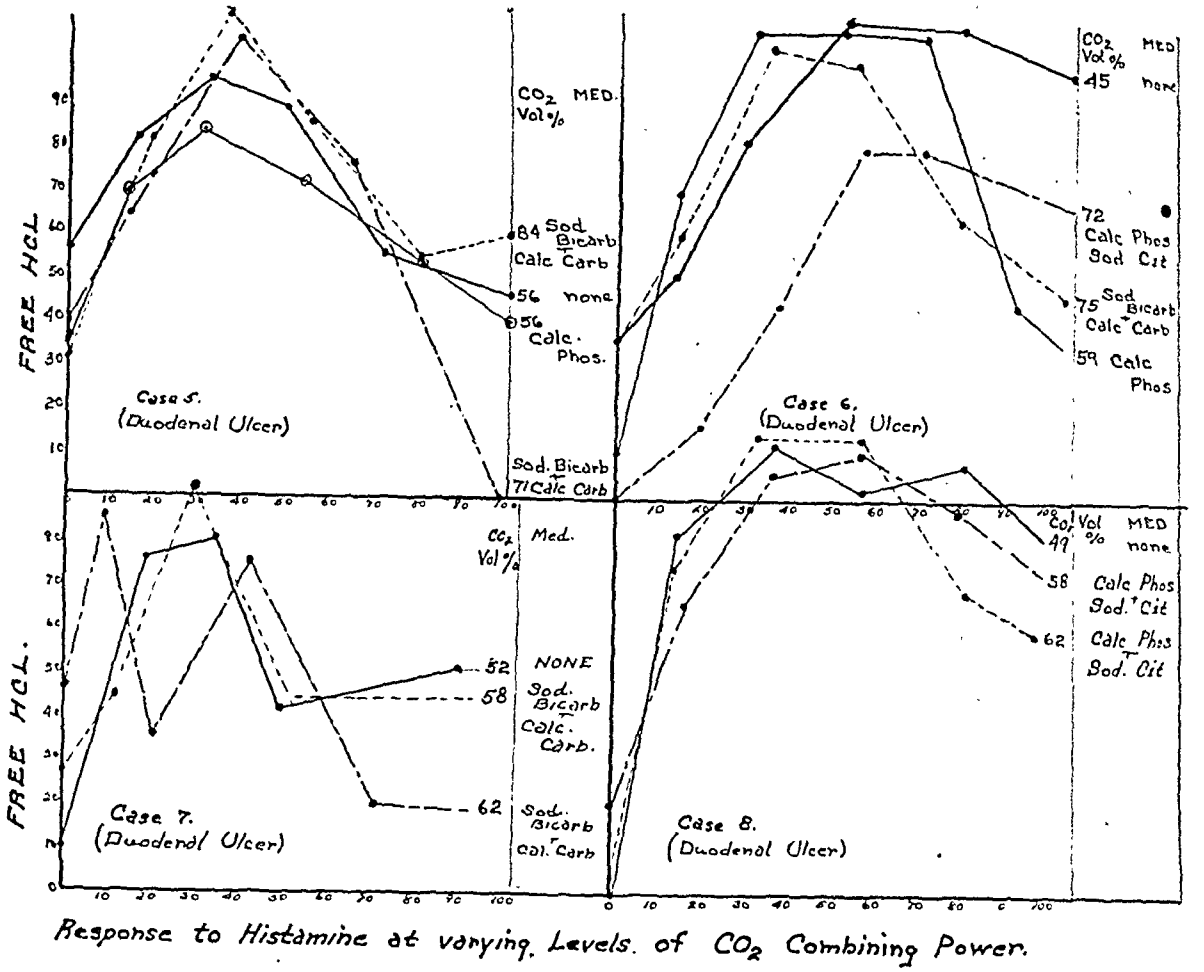


Fig. 4

5. Figure 1, shows the result of sodium bicarbonate ingestion with limited fluids. Although true alkalosis did not develop there was an enormous increase in base which is held combined with protein and organic acids, leaving the sum total of chlorides and bicarbonates practically unchanged. Fluids, therefore, deserve much consideration in the prevention and treatment of alkalosis.

While gastric hypersecretion is apparently one of the basic factors promoting alkalosis, it is possible that there may be a reciprocal action and that changes in the chemistry of the blood influences the activity of the gastric glands. It is occasionally noted clinically that patients taking alkalis have higher acid secretion than before treatment was started. In 1918, Crohn (8) demonstrated that alkali produced an irritative secretory reaction in the stomach. More recent experiments suggest that alkali may also act in an indirect manner to increase gastric acidity.

The gastric secretion of acid has been shown to be augmented by the inhalation of CO_2, (Bakaltschuk (9)) by the intravenous injection of sodium bicarbonate (Szilard (10)) and by pathological conditions causing a rise in plasma CO_2 (Apperly (11)).

In 1932, Browne and Vineberg (12) working with dogs, showed that the total amount of acid secreted could be increased or decreased by artifically raising or lowering the plamsa CO_2 content. Apperly and Crabtree (13) believe that in human subjects certain considerations suggest direct relationship between the concentration of gastric hydrochloric acid and the plasma bicarbonate content. There appears to be an agreement among investigators that the relationship is with the CO_2 content and not with the pH of the plasma.

In this investigation a group of ulcer patients has been studied to determine the reaction of the gastric secretion to various stimuli in the presence of varying levels of plasma CO_2 induced by the use of alkalis.

When the Ewald meal was used as a gastric stimulant, it was found that some cases, at least, did show a somewhat higher acidity curve when the plasma CO_2 was appreciably elevated. (Figure 3).

With histamine as a secretory stimulant there was less difference between the acidity curves produced at varying CO_2 levels. (Figure 4).

An alcohol test meal gave curves which if anything were lower when the CO_2 was elevated. (Figure 5).

However, gastric analyses in which only the concentration of acid is measured, are subject to uncontroll-

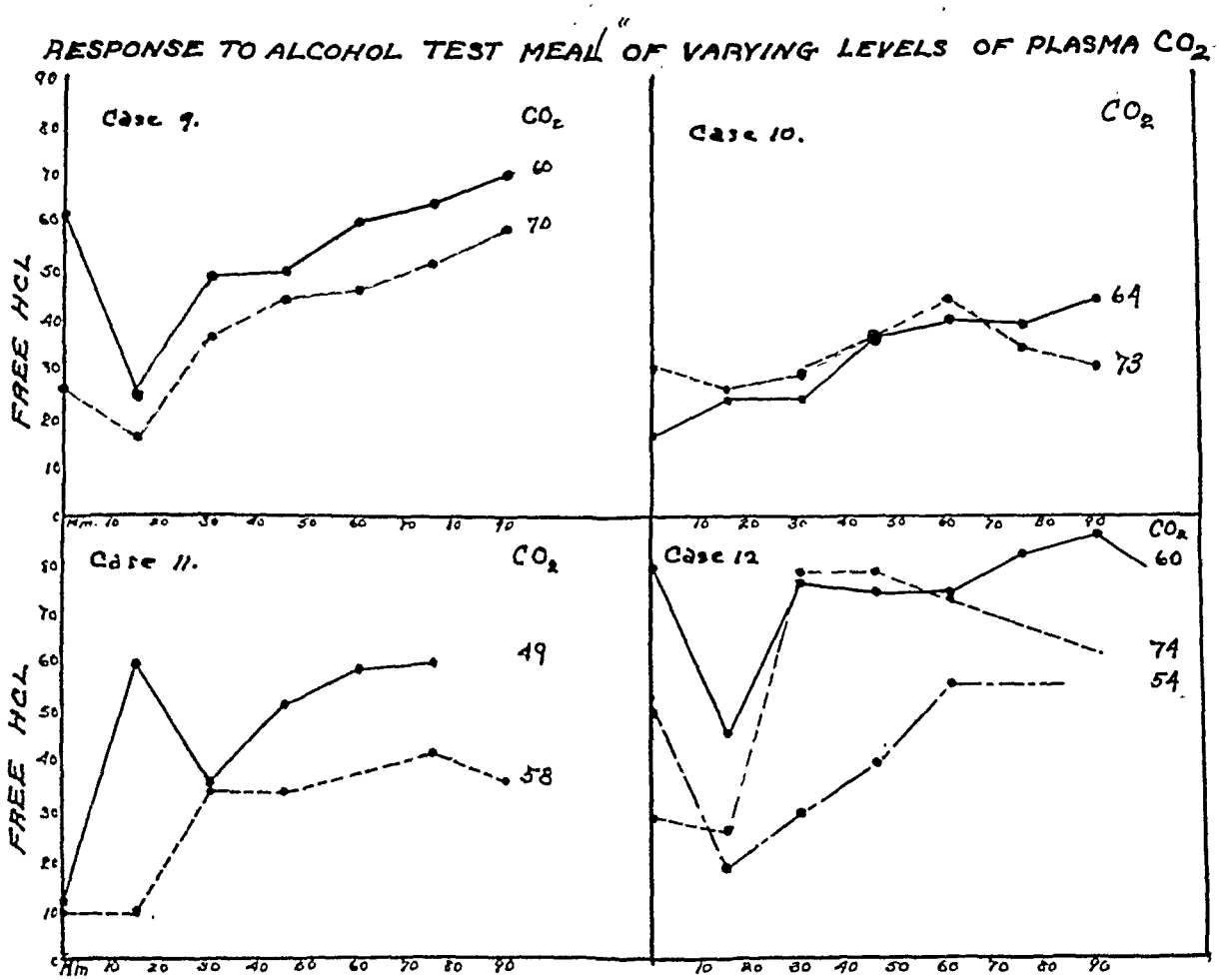


Fig. 5

able variations related chiefly to factors of dilution and emptying of the stomach during the test. It seems more important to determine the total quantity of acid secreted in a given time. This was done in the case of histamine stimulation by aspirating the entire stomach contents every ten to fifteen minutes so that there was comparably little accumulated secretion to be expelled through the pylorus. The product of the volume secreted and the concentration of acid gives the total quantity of acid in a given time. When the alcohol test meal was used, the rate of dilution of an added dye was measured colorimetrically and the volume secreted was calculated according to the method of Bloomfield (14).

The results of the calculations show that in 7 out of 11 cases there is no corresponding increase in acid secretion as the CO_2 is elevated, but that the tendency is definitely in the opposite direction. (Figure 6).

The apparent contradiction to Browne and Vineberg's results may be explained by the fact that their work was an acute experiment with dogs in which the changes in the CO_2 levels were enormously greater than are available in a clinical study.

SUMMARY

In a study of the electrolytes of the blood can be found an explanation for the clinical fact that alkalosis occurs most readily in cases with active ulcers and high gastric secretion; i.e., the secretion and neutralization of excessive quantities of hydrochloric acid is as much a factor in raising the CO_2 as is renal impairment.

Under clinical conditions, there is a direct relationship between the activity of gastric secretion and the degree of change in the plasma CO_2 produced by alkali therapy. On the other hand, there is little evidence that shifts in blood electrolytes, including an elevation in CO_2, appreciably affect gastric secretion except for some tendency to decrease the quantity of hydrochloric acid secreted by the stomach in a unit time.

Laboratory experiments which indicate that gastric secretion is augmented by any increase in blood CO_2, are not confirmed under clinical conditions, at least to a degree which would contra-indicate the use of alkali in the treatment of ulcer.

METHODS

In the study of the blood the total base was determined by the method of Van Slyke, Hiller and Berthelsen (15); the CO_2 content by the method of Van Slyke and Neill (16); the chlorides according to Wil-

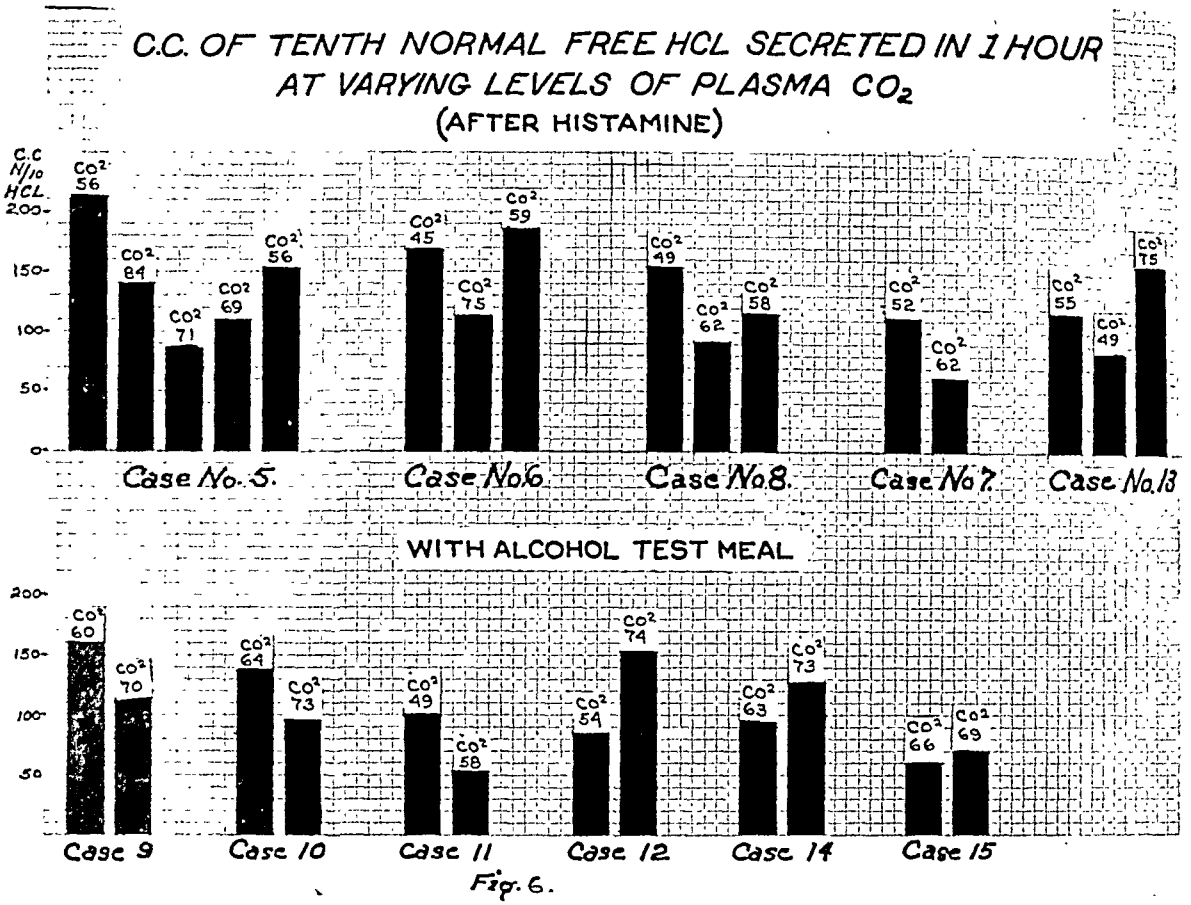


Fig. 6.

son and Ball (17); and the pH of the plasma by the colorimetric method of Cullen (18) with the use of "permanent" color standards. The blood for analysis was drawn from the vein without stasis and with protection from the air by the use of mineral oil. Neutral potassium oxalate was used to prevent clotting and the specimen was centrifuged immediately to obtain plasma for the pH, CO_2 and chloride determinations. Part of the specimen was allowed to clot and the serum was used for the estimation of the total base.

In the study of gastric secretion, the stimulants used were the standard Ewald bread and water meal, subcutaneous histamine in doses of 0.5 to 1.0 mg. depending upon the size of the patient, and 100 c.c. of 7% alcohol. In every case fractional methods were used with an indwelling Rehfuss' tube and the patient lying on his back to promote retention of the gastric contents in the fundus. Patients were instructed not to swallow saliva during the test. Specimens were taken at intervals of from ten to twenty minutes. The tests were carried out eleven to twelve hours after the last powder.

When the Ewald meal was used 10 c.c. specimens were removed for analysis. With histamine the stomach was completely emptied at the end of each test period. The volume of the secretion as well as the acid concentration was recorded in order to calculate the total quantity of free HCl secreted in a measured time. With the alcohol test meal phenolsulphonphthalein was added to the 7% alcohol solution. At the end of each fifteen minute period the entire contents of the stomach were removed, the volume measured and immediately returned to the stomach with the exception that 20 c.c. were withheld for the estimation of free HCl and concentration of dye by colorimetric comparison with the original solution. The method and calculations have been described by Bloomfield and Keefer (14). The total acid secreted in a period of time was calculated as the difference between the quantity of acid introduced into the stomach at the beginning of the period and the quantity of acid present at the end of the period plus the quantity of acid lost by evacuation during the period. The volume of gastric contents evacuated is determined by adding the volume secreted during the period to the volume introduced at the beginning of the period and subtracting the volume found in the stomach at the end of the period.

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DISCUSSION

DR. HENRY A. RAFSKY (New York, N. Y.): Upon a previous occasion the fact was emphasized that patients with obstructive peptic ulcers were potential cases of alkalosis; furthermore that they could be successfully treated by comparatively small doses of alkali. This raised the question as to whether hyperchlorhydria and hypersecretion, while valuable as diagnostic aids in peptic ulcer, were equally as valuable as therapeutic guides.

With this in mind, I took a small series of cases of the duodenal ulcers and to one group I gave various antacids and another group hydrochloric acid, minims 25 to 30 t.i.d., a.c., using histamine to determine the acid curve before the treatment was started and before the patients left the hospital. It was interesting to note that there was no material relationship between the secretory and the clinical response, in either group. In some of the patients, to whom antacids were given, there was a downward trend to the curve; the same was noted when hydrochloric acid was administered. In others the acid curves were just as high after the treatment as before the treatment, even though they were symptom free and irrespective of the medication used.

I am not advocating hydrochloric acid as a therapeutic measure. It was only used as a control. These observations indicate that, perhaps, our notions on the relationship of hyperchlorhydria and the use of large doses of alkali are perhaps too fixed and may be subject to change. Some of the charts of these patients are being presented at the Scientific Exhibit, at the gastro-enterological section.

Observations on Gastric Acidity Before and After Development of Carcinoma of the Stomach*

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WHEN the Ewald meal is used, achlorhydria is detected in about 60 per cent of the cases of cancer of the stomach in which operation is performed, and hypo-acidity characterizes the gastric secretion in a majority of the remaining cases (1)**. For some reason the percentage of anacidity (20) and the mean concentration of free hydrochloric acid (38) found among normal persons of the same sex and age have been respectively increased to 60 per cent and reduced to 26 clinical units among cancerous persons. When does this reduction in gastric acidity take place? Do persons who subsequently develop gastric cancer start life with a low mean secretory capacity, or do they start life with a normal secretory capacity that is partly lost before cancer develops, or does the reduction take place after cancer develops? What is responsible for the loss of secretion? It is our plan to present data of our own and to review those of other observers bearing on these problems.

MATERIAL

Search of our records has disclosed seventy-nine cases in which analysis following a gastric test meal was carried out before and after the development of carcinoma of the stomach. Patients of all ages, from the third to the eighth decades of life, were seen at both the first and the second admissions. At the first admission, the ages of six fell in the third; of sixteen, in the fourth; of nineteen, in the fifth; of thirty, in the sixth; of seven, in the seventh, and of one, in the eighth decade of life. At the second admission, the ages of three fell in the third; of eight, in the fourth; of eighteen, in the fifth; of twenty-five, in the sixth; of twenty-one, in the seventh, and of four in the eighth decade of life. The average ages of the patients at the time of the first test meal, and before the development of cancer, was forty-seven years and at the time of the second admission, and after the development of cancer, fifty-three years.

Twenty-one of the seventy-nine patients were operated on at the time of the first admission. Lesions of the stomach were removed and found to be benign in fourteen cases. Cholecystitis was found in another four, and duodenal ulcer in another two cases. In each of these six cases, as well as in a seventh case, the stomach was examined at the time of operation and was found to be free of organic disease. In these twenty-one cases in which operation was performed a

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**The percentage of cases of achlorhydria varies from 50 to 90 in different series, depending on the selection of cases (2, 3, 4, 5).

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cancer was almost certainly absent at the time of the first admission. In most of the remaining fifty-eight cases, the proof that a cancer did not exist at the time of the first test meal was almost as good. One or more roentgenologic examinations of the stomach were conducted in forty-nine of the fifty-eight cases. In forty-five of the forty-nine cases roentgenologic examinations failed to disclose a lesion of the stomach. In one, the roentgenologic diagnosis was indeterminate; in another, the roentgenologic diagnosis was gastric ulcer, while in two more, the roentgenologic diagnosis was duodenal ulcer. In the last four cases mentioned, the intervals between the first examination and the examination which disclosed cancer were, respectively, seven, three, two, and two years, intervals almost too long for a cancer of any size to exist at the time of the first test meal. In these forty-nine cases in which roentgenologic examination was made, the evidence was definitely against the presence of cancer at the time of the first test meal. In the remaining nine of the fifty-eight cases roentgenologic examination was not carried out, but eighteen, fifteen, eleven, ten, ten, four, three, three, and one years passed after the first test meal before cancer was diagnosed. It is possible that a cancer was already present in the last case, in which an interval of only one year passed between the two examinations, but this patient was in good health, had no gastric complaints, and the test meal was done because the patient, knowing he had had gastric anacidity for years, wanted this checked. In the remaining eight of the nine cases in which a roentgenologic examination was not made, the interval itself eliminates the possibility of a cancer being present at the initial examination. In short, the surgical findings, the roentgenologic examinations, or the time intervening between the first and second examinations make it improbable that a cancer existed at the time of the first examination except in a small percentage of cases and, if present, that it was large enough to affect gastric acidity per se.

METHODS

Modification of the Ewald meal used in determining gastric acidity in this series has been described elsewhere (1). In the presentation of the data culled from these records, the statistical technic of Vanzant, Alvarez, Eusterman, Dunn and Berkson has been followed (6).

GASTRIC ACIDITY BEFORE THE DEVELOPMENT OF CARCINOMA OF THE STOMACH

Of the seventy-nine patients the gastric contents of thirty (38 per cent) were achlorhydric before cancer developed (Table I). Particular attention is called to this figure inasmuch as it will be interesting to remember it at a later time. In the remaining forty-nine or 62 per cent of the cases, the gastric contents contained free acidity of a mean concentration of 27.1 clinical units. In other words, even before cancer had developed the incidence of achlorhydria was greater by 22.1 per cent, and the mean free hydrochloric acid was less by 14.2 units, than that expected for a group of persons of the same sex and age. Either these seventy-nine persons started life with an average gastric acidity below normal or they started life with a normal gastric acidity that was subsequently reduced by some abiotrophic or inflammatory process by the time they had reached the average age of forty-seven years.

GASTRIC ACIDITY AFTER THE DEVELOPMENT OF CARCINOMA OF THE STOMACH

Between the time of the first admission (before the development of cancer) and the time of the second admission (when cancer was diagnosed), an interval of one to eighteen years elapsed (Table 2). Within five years after the first admission forty-seven, or more than half of the patients of this series had developed carcinoma of the stomach. Within six to ten years inclusive, an additional twenty patients had developed cancer. In another group of nine patients, eleven to fifteen years passed before cancer manifested itself clinically, while in the remaining three cases, sixteen to eighteen years rolled by before the disease appeared. The interval averaged six years and by this time the mean age of the patients had increased from forty-seven to fifty-three years.

TABLE II

Intervals in years between the first admission and the development of gastric cancer, cases

Interval, years	Group I	Group II	Group III	Total
1	5	1	9	15
2	4	3	1	8
3	4	3	3	10
4	3	3	3	9
5	2	2	1	5
6	1			1
7	1	2	2	5
8	4	1		5
9		1	1	2
10	3	1	3	7
11	1		2	3
12		1	1	2
13		1		1
14		1		1
15	1		1	2
16	1		1	2
17				
18		1		1
Totals	30	21	28	79
Mean interval	5.4	6.5	5.5	5.8

Definite changes occurred in the secretory activity of the seventy-nine patients in the interval between examinations. The percentage of patients who had achlorhydria had increased from 38 to 64.6 and the number of patients whose gastric contents contained free acid decreased from forty-nine to twenty-eight (Table I). The mean free acidity in the twenty-eight cases was 30.3 units. It is interesting to note that the concentration of acid was higher than that of the

forty-nine persons who had free acid in the stomach six years previously.

The seventy-nine patients can be divided into three groups according to the behavior of the gastric secretory activity in the interval between the first test meal and the second test meal (Table I). Group I includes thirty patients whose gastric contents were anacid at the time of the first test meal and remained so at the time of the second meal. Hurst (7) stated that he had seen five patients who were known to be achlorhydric before carcinoma developed and had found records of at least twenty-two similar cases. Konjetzny (8) stated that Albu, Boas, Kuttner, Porges, Stewart, Zweig and others, as well as Hurst, had observed that cancer developed after the appearance of achlorhydria. Obviously, it is not uncommon for achlorhydria to precede the development of cancer. Group II includes twenty-one patients whose gastric content contained free acid at the time of the first meal but not at the time of the second. Konjetzny has reported a similar case. Group III is composed of twenty-eight patients whose gastric contents contained free acid at the time of the first, and retained it at the time of the second test meal in spite of the development of cancer of the stomach. Hurst (9) reported three similar cases.

In the secretory activity of stomachs of the twenty-one patients of Group II are to be found the changes that have so altered the percentage of anacidity at the time of the second test meal from that found at the time of the first test meal. The mean free hydrochloric acid of these twenty-one patients at the time of the first test meal was 23.9 or 17.4 units less than that expected of a group of normal persons of the same age and sex (Table I). The mean concentration of free hydrochloric acid of the twenty-eight patients of Group III at the time of the first test meal, and who continued to secrete free acid after the development of cancer was 29.4 or only 11.9 units below that expected in a group of normal persons of the same sex and age (Table I). In other words, the secretory activity of the stomachs of the patients of both Groups II and III was subnormal even before the development of cancer. This suggests that some process reducing gastric secretory activity was already at work in these cases of Groups II and III at the time of the first test meal.

Seven of the patients of Group II had undergone gastro-enterostomy for benign gastric ulcer at the time of the first admission. The remaining fourteen patients were not subjected to operative procedures or to operative procedures that reduced gastric acidity. In the seven cases in which gastro-enterostomy was performed, the reduction in gastric acidity may well be attributed to the gastro-enterostomy, although this is not necessarily true, for gastro-enterostomy often fails to reduce gastric acidity to the extent of achlorhydria (10, 11). In at least fourteen cases something other than the surgical procedure reduced the gastric acidity to the point of achlorhydria.

The free acidity in the fourteen cases in which gastro-enterostomy was not performed was 21.7 units or 20 units below the average for normal men and women of the same age at the time of the first test meal. The average secretory activity both of all the patients of Group II and of the fourteen patients of Group II who were not subjected to gastro-enterostomy was less vigorous than that of those in Group III, even before the development of cancer of the stomach. Since free acid was lost from the gastric contents of the patients of Group II but was retained in the gastric contents of the patients of Group III, it seems that the more nearly normal the concentration of free hydrochloric acid, and the more vigorous the secretory activity before the development of cancer, the less likely that it will be absent when cancer develops.

The free acidity of ten patients of Group II was between 1 and 19; of seven, between 20 and 39; of three, between 40 and 59, and of one, between 60 and 79. The free acidity of five patients of Group III was between 1 and 19; of thirteen, between 20 and 39, and of ten, between 40 and 59. In other words, concentrations of free hydrochloric acid from 6 to 60 units were noted in Group II, yet all patients lost their free acid. Con-

TABLE I

Mean age, mean free hydrochloric acid, and percentage of achlorhydria of seventy-nine patients before and after the development of carcinoma of the stomach

	First admission								Mean interval, years	Second admission						
			Achlorhydria			Free acidity				Achlorhydria				Free acidity		
			Patients								Patients					
Group	Total patients	Mean Age, Years	Number	Per cent	Comparison with normal	Patients	Mean, units	Comparison with normal		Mean age, years	Number	Per cent	Comparison with normal	Patients	Mean, units	Comparison with normal
Total	79	47.1	30	38	+22.1	49	27.1	—14.2	5.8	52.9	51	64.6	+48.7	28	30.3	—9.8
I	30	49.3	30	100					5.4	54.7	30	100				
II	21	42.9				21	23.9	—17.4	6.5	49.4	21	100				
III	28	48				28	29.4	—11.9	5.5	53.5				28	30.3	—9.8

Group I—Patients with achlorhydria at both admissions.
Group II—Patients with free acidity at first, and achlorhydria at second admission.
Group III—Patients with free acid at both admissions.

centrations of free acid from 6 to 46 units were noted in Group III, yet all patients retained their free acid. Apparently, higher degrees of free acidity are lost just as well as the lower degrees and lower degrees are retained just as well as the higher degrees when cancer develops. Lower degrees are lost more frequently than higher degrees.

THE LOSS OF GASTRIC ACIDITY A SELECTIVE AFFAIR

The loss of gastric acidity is a selective affair; gastric acidity was lost in all cases of Groups I and II and retained in those of Group III. While the mean free acidity of the patients of Group III was practically the same on the first and second admissions, in four cases the concentration of free acid remained unchanged; in fifteen, it decreased an average of 10 units (extremes 4 and 18 units), and in nine, it increased an average of 20 units (extremes 4 and 60 units). While the variations in Group III, in a general way can be ascribed to the variations in the response to the test meal, it still seems clear that the concentration of free acid is reduced in some and retained in other cases. The process responsible for the reduction of gastric acidity attacks the mucosa in some cases but not in others.

WHEN DOES THE LOSS OF GASTRIC ACIDITY OCCUR?

It is commonly believed that the low gastric secretory activity characteristic of carcinoma of the stomach appears before the development of cancer. Little evidence other than the observation of achlorhydria in a few cases in which cancer developed subsequently has been advanced. We, too, have reported cases in which achlorhydria existed before the development of cancer but we also have shown that the percentage of achlorhydria is above normal and the mean concentration of free acid below normal at an average of six years prior to the diagnosis of cancer (Table I). We also have shown that the secretory activity falls further below normal in the interval between the first examination and the diagnosis of cancer (Table I). The gastric contents of twenty-one patients contained free acid at the time of the first examination but had become achlorhydric at the time the diagnosis of cancer was made. Unfortunately, test meals were not employed in the interval between the two admissions in these cases and, so far as the data go, the development of achlorhydria may have taken place in the interval between the first admission and the development of cancer or after the development of cancer but before the second admission. A depression of gastric acidity occurred also in some of the cases of Group III but not to the point of achlorhydria. In some of these cases test meals were done in the interval between the first admission and the diagnosis of cancer. In these cases the depression of gastric acidity occurred before the development of cancer. The following case is an example:

Case 1. A man fifty years of age registered at the clinic May 17, 1921, giving a history characteristic of ulcer of twelve years' duration. The Ewald meal revealed free acidity of 28 at the end of the first hour. Roentgenologic examination of the stomach disclosed a small ulcer on the lesser curvature. Excision of the ulcer by cautery was carried out and the pathologic diagnosis was benign ulcer. The ulcer measured 0.75 cm. in diameter and was situated high on the lesser curvature, above the incisura.

The patient returned September 20, 1926. Symptoms had recurred one year prior to registration. Fractional analysis after the Ewald meal revealed no free hydrochloric acid at the end of an hour, an hour and fifteen minutes, and an hour and a half, and only 10 units at the end of an hour and forty-five minutes. The roentgenogram again gave evidence of a small ulcer on the lesser curvature, at the angle. The ulcer was excised and a Mayo type of pyloroplastic gastroduodenostomy was performed. The ulcer was situated on the lesser curvature about 2¼ inches (5.5 cm.) above the pylorus. The pathologist reported a simple gastric ulcer.

The patient returned again January 30, 1930. Symptoms had recurred six months previously. Analysis after the Ewald meal revealed free hydrochloric acid with a concentration of 10 clinical units. The roentgenogram gave evidence of an operable carcinoma at the pyloric end of the stomach. Anterior gastro-enterostomy was performed for a perforating carcinoma of the posterior wall just above the pylorus with extension up to the angle. The patient died of carcinoma in February, 1931.

In this case the depression of gastric acidity cannot logically be ascribed to the carcinomatous process that ultimately developed.

We are inclined to believe that the loss of gastric acidity in the twenty-one cases of Group II also occurred before the development of cancer. The cancers of the patients of Group II were, for the most part, too small to affect gastric acidity per se. The general statement that loss of gastric acidity occurs for the most part before cancer develops appears to be a conservative one.

A study of the time intervals between the first and second test meals, and of the gastric acidity of the three groups, develops some interesting points. In the first place, the achlorhydria of cancer may be present at an early age. It was known to be present in two of our cases before the age of thirty years. In the second place, anacidity may exist many years before the development of cancer. It existed one to five years in eighteen cases, six to ten years in nine cases, eleven to fifteen years in two cases, and as long as sixteen years in one case in Group I before the diagnosis of cancer was made (Table II). Even more interesting is the appearance in Group II of achlorhydria in one case within a period of one year, in three cases within a period of two years, in three cases within a period of three years, in three cases within a period of four years, and in two cases within a period of five years preceding the diagnosis of cancer (Table II). The loss occurs at any age and at long and short intervals before the development of cancer. Obviously, the achlorhydria which precedes the development of cancer of the stomach is not an immediate precursor of cancer of the stomach nor is it always attributable to a developmental defect in the mucous membrane of the stomach destined to become ultimately a seat of cancer.

It may well be asked whether a depression of gastric acidity follows also the development of gastric cancer. This question may be answered in the affirmative. Shay and Schloss (12), Robertson (13), Koch (14) and Bockus, Bank and Willard (15) have recorded cases in which a depression of gastric acidity has occurred after the development of cancer. In these cases gastric acidity was actually observed to fall as the

disease progressed. The frequency of reduction in gastric acidity following the development of gastric carcinoma is unknown. On the other hand, gastric acidity may actually rise. In nine cases of Group III free gastric acidity was higher after than before carcinoma developed. Hurst (7) has seen gastric acidity behave in a similar way in a carcinomatous stomach.

WHAT IS RESPONSIBLE FOR THE REDUCTION IN GASTRIC ACIDITY?

Achlorhydria and all degrees of free acidity occur in childhood and young adulthood. Achlorhydria (16, 22) occurs in about 4 or 5 per cent and hypochlorhydria in about 10 per cent of cases. Three major hypotheses have been advanced in explanation of the variations of gastric acidity in childhood and young adulthood. The first hypothesis observes that these variations are constitutional and are present at birth, and that achlorhydria and hypochlorhydria are the results of developmental defects in the secretory mechanism. The second hypothesis assumes that the hypochlorhydria and achlorhydria are attributable to abiotrophic changes in the acid secreting cells that appear after birth. The third hypothesis assumes that achlorhydria and hypochlorhydria are attributable to destruction of the acid secreting cells by an inflammatory process, a gastritis. The advocates of the constitutional hypothesis point to the familial and hereditary nature of achlorhydria or pernicious anemia, shown by the studies of Hurst (23), Wilkinson and Brockbank (24) and Conner (25), as proof that such developmental defects occur. Conner thought it unlikely that the achlorhydria itself is inherited but that the tendency to development of this condition later in life is an inherited factor. Observations of the type reported by Rozendaal and Washburn (26) add weight to such a belief. These authors reported two cases of pernicious anemia in which the concentration of free acid in the gastric contents was 34 and 16 clinical units respectively, nineteen and seventeen years before the development of pernicious anemia. In these two cases at least the anacidity of pernicious anemia was not present at birth and therefore was not the result of a constitutional defect present at birth. The advocates of the hypotheses of constitutional defect and abiotrophy point out that the subnormal secretory states are unassociated with symptoms and for this reason do not represent a disease process. However, the advocates of chronic atrophic gastritis as the cause of subnormal secretory states remind us, on the other hand, that gastritis occurring in the earlier years of life causes reduction of gastric acidity, and that this reduction is symptomless. They believe it is just as reasonable to explain the lower grades of acidity and anacidity on the basis of gastritis as on the basis of developmental defect. The demonstration by Faber (27) and others that changes in the gastric mucosa seen in pernicious anemia exhibit characteristics of a chronic inflammatory process at times without atrophy, and the report of Hurst (28) on the restoration of gastric secretion in pernicious anemia by treatment of gastritis are impressive evidences that chronic gastritis and not a constitutional defect is responsible for changes in gastric secretion in pernicious anemia. Final acceptance of the hypothesis of defect will await the pathologic examination of a number of stomachs removed from infants. At the present time the advocates of an inflammatory origin seem to have a little the best of the argument.

Achlorhydria and all degrees of free acidity likewise occur in middle and old age in normal men and women. Vanzant, Alvarez, Eusterman, Dunn and Berkson (6) using the Ewald meal have demonstrated that the percentages of achlorhydria greatly increase with age in both normal men and women, the percentage of achlorhydria reaching about 26 at the age of seventy years. They have shown likewise that mean free acidity in men is in the neighborhood of 47 units between the ages of twenty and forty years and that thereafter it decreases to a mean of 33.5 units at the age of seventy years; in women the mean free acidity remains remarkably constant at about 33 units at all ages. Polland and Bloomfield (29) have noted the same behavior in gastric acidity when histamine is used as a stimulant. This depression of gastric acidity that occurs with advancing years may be the result of either abiotrophy or an inflammatory process. Alvarez (30) has commented on the fact that the mean acidity of women does not fall off with advancing years. He believes that this makes it unlikely that the decline of gastric acidity is attributable to slow atrophy of the gastric glands, because one would expect age to work the same injury to women as to men. Although there is little direct proof that an abiotrophic process is the cause of the decline of gastric secretion with advancing age, it is an attractive idea. On the other hand, chronic atrophic gastritis is a visible, tangible explanation for the decline. The realization that chronic gastritis and not always a developmental defect plays a rôle in the development of the achlorhydria of pernicious anemia and the recognition that chronic gastritis causes a depression of gastric acidity and even to the point of anacidity in all years of life without producing symptoms, have been the important steps taken toward the acceptance of chronic gastritis as an important cause of achlorhydria. Faber (27) has gone so far as to say, "When one microscopically examines the mucous membrane of the stomach after proper fixation, one always finds in patients with chronic anacidity, very pronounced signs of chronic inflammation and first and foremost, a diffuse gastritis tending to atrophy, a pangastritis."

The subnormal gastric secretory activity present in our seventy-nine cases before the development of carcinoma of the stomach may be attributable to any one of the causes believed responsible for subnormal secretory activity in the general population. The same evidence may be cited in support of, and against, the acceptance of each of them. Until gastric acidity has been followed from childhood to the appearance of cancer, the number of cases of anacidity or hypoacidity possibly attributable to a developmental defect of the gastric glands will be unsettled. It is possible that cancer is more prone to develop in patients with a constitutional defect in the secretory mechanism or in those whose mucous membrane atrophies with the passage of years than in persons with a normal mucous membrane. In this way the high incidence of achlorhydria and of hypochlorhydria in persons destined to develop gastric cancer may be explained. However, certain pathologic evidence may be cited against the acceptance of the hypothesis involving the concepts of either a constitutional defect or of a non-

inflammatory atrophy or abiotrophy, and in favor of the hypothesis of inflammation. In the first place, chronic gastritis seems usually to be associated with the achlorhydria of gastric cancer. Orator (31), using the Ewald meal, found achlorhydria in seven of eight cases of so-called primary cancer and free acid in twelve of fourteen cases of so-called ulcer-cancer. Microscopic examination of the mucous membrane of the stomachs of twenty patients with primary cancer disclosed atrophic gastritis involving the fundus as well as the pyloric region, pangastritis, in nineteen. Microscopic examination of the stomachs of eight patients with ulcer-cancer revealed a well-marked gastritis involving the pyloric region in eight cases but a perfectly normal mucous membrane of the fundus in five, slight gastritis of the fundus in two, and severe gastritis of the fundus in only one of the eight. In other words, diffuse atrophic gastritis involving the mucous membrane of both the antrum and the body was found in cases of cancer with achlorhydria while marked gastritis, involving the mucous membrane of only the antrum, was found in those cases in which free acid was present. Baker (32) has studied the mucous membrane of the fundus in fifty cases of carcinoma of the stomach. In fifteen, or 30 per cent of these cases the presence of free hydrochloric acid was revealed by the Ewald test meal before operation. Of these fifteen patients, Baker found eight to have a normal distribution of acid cells in the fundus and seven to have decreased acid secreting cells. In the remaining thirty-five cases in which free acid was not found in the gastric contents, acid cells were not found in the fundus in twenty-seven cases and only occasional acid cells in eight cases. Baker also examined microscopically the mucosa made available in this series by gastric resection. Resected specimens from nine patients of Group I, from seven patients of Group II, and from ten patients of Group III were sectioned and stained. Care was exercised to take sections at least 5 cm. from the growth. In Group I, the mucous membrane of the upper portion of the antrum or of the lower portion of the body of the stomach gave evidence of marked atrophic gastritis, usually with lymphocytic inflammation, metaplasia, hypertrophy, or atrophy. The acid cells were usually few. It is to be noted that gastritis involved the gastric mucous membrane of the only group of patients whose achlorhydria could possibly be attributable to a defect in the mucous membrane present at birth. In Group II the mucosa of the upper portion of the antrum or the lower portion of the body gave evidence of moderate or marked gastritis, usually with only fair preservation of the acid cells in five of the seven cases. In the remaining two cases, the mucous membrane of the body appeared to be normal. Gastroenterostomy had been performed for gastric ulcer before the development of cancer in these two cases. In Group III the mucosa of the upper portion of the antrum or the lower portion of the body of the stomach gave evidence of slight or moderate gastritis in eight of the cases, while the mucosa of the body was normal in three. Gastritis was marked in the antrum in one case in which it was absent in the body. These pathologic studies of Orator (31) and Baker (32) show that chronic gastritis of marked degree, involving the acid secreting portion of the stomach, is usually present when achlorhydria is present and that it is usually absent when free hydrochloric acid is secreted. They show, further, that the acid secreting cells are absent or reduced in number when achlorhydria exists and are present in good numbers when acid is secreted. Such findings point to chronic gastritis as a cause of the destruction of the acid cells and not to a developmental defect or a degenerative, noninflammatory process. Advocates of the constitutional hypothesis will take the position that a subnormal mucous membrane is more prone to injury and to the development of gastritis than a normal mucous membrane and that the gastritis may not be the cause of the low secretory activity. While it is reasonable to believe that a subnormal gastric mucous membrane is susceptible to injury and to the development of gastritis, it is difficult to discount the effect of such marked inflammatory changes on the secretory activity of the mucous membrane. Pathologic evidence seems to point overwhelmingly to chronic gastritis as an important cause of the depression of gastric acidity in cases in which persons are destined to develop carcinoma of the stomach.

The further decrease in gastric acidity seen in patients of Group II, in the interval between the first and second meals, occurred after they had reached adult life. In these cases at least, a developmental defect present at birth was not responsible. Either abiotrophy of the mucous membrane or an inflammatory process was responsible. Again, the importance of the gastritis as a cause of the depression cannot be discounted.

Progression of degenerative or chronic inflammatory changes already present in the gastric mucosa before the development of gastric cancer explains satisfactorily the further loss of gastric acidity observed by Koch (14), Shay and Schloss (12), Bockus, Bank and Willard (15), and Robertson (13) after the development of gastric cancer. But there is another possible factor in the depression of gastric acidity after the development of cancer; namely, the cancer itself. Certain statistical data point to a relationship between the mean size of the cancer and the secretory activity of the stomachs of patients with gastric cancer. Thus Eusterman and Bueermann found in their study that the percentage of anacidity, which was only 49 per cent in cases of resectable cancer, increased to 77 per cent in the cases in which exploration was carried out but resection was not done and further increased to 93 per cent in the frankly inoperable cases. Comfort and Vanzant studied the relationship between the size of resected cancers and the mean secretory activity. They found that in cases of gastric cancer in which the cancer was 3 cm. or less in diameter, the mean free acidity and the incidence of achlorhydria were practically the same as for a group of normal persons, being 38 units and 17.5 per cent respectively, but that the larger the cancer was, the lower the mean free acidity and the higher the incidence of achlorhydria; the percentage of achlorhydria rose to as high as 90, and the mean free acidity fell as low as 10 clinical units when the lesion was 10 cm. or more in diameter. These statistical studies suggest that the growth of the tumor depresses gastric acidity. However, a study of the relationship between gastric acidity and the size of the cancer in the forty-two cases of this series in which resection was carried out and the size of the tumor reported by

the pathologist, invites another interpretation of the data. The forty-two cases may be divided into three groups: the fourteen patients of Group I had no free hydrochloric acid in the gastric contents at the time of the first admission; the ten patients of Group II had free hydrochloric acid averaging 20 units at the time of the first admission but none at the time of the second; the eighteen patients of Group III had free hydrochloric acid averaging 34.4 units at the time of the first admission, and this concentration had not materially changed at the time of the second. The cancers had attained average sizes of 55.7, 39.8, and 22.7 sq. cm., respectively, in the three groups. In other words, the larger cancers were found in stomachs that were known to be achlorhydric before the development of cancer. This could mean that cancer grows larger before symptoms lead the patient to submit to examination when achlorhydria is known to have been present before the development of cancer than when free hydrochloric acid is known to have been present.

While statistical evidence that the cancer itself has a depressing influence on the secretory activity of the cancerous stomach is inconclusive, it is not unreasonable to believe that this is at times so. It is conceivable that cancer can depress gastric acidity in several ways: 1. By destruction of acid secreting cells in sufficient number to reduce the volume of acid secreted; cancers of the body and fundus of the stomach are not infrequently large enough to destroy an area of gastric mucosa sufficient to reduce the volume of acid secreted. 2. By increasing the amount of neutralizing fluid in the stomach by the exudation of serum from the surface of the tumor; among others, Crohn (33) has mentioned this possibility. 3. Experimental and clinical evidence exists showing that vitamin deficiency may depress gastric secretion. Webster and Armour (34) found in dogs fed on a diet deficient in vitamin B a great impairment of secretory response to sham feeding, to the subcutaneous injection of histamine, and to introduction into the small intestine of food in 5 per cent alcohol, and that complete restoration of gastric secretion occurred within three days after addition of powdered yeast to the diet. Cowgill and Gilman (35) obtained similar results and concluded that "so far as any diminution of gastric secretion occurs during the regimen of lack of vitamin B complex, this is due to the absence of B_1." Odin (36) expressed the belief that deficiency of vitamin B explains the higher incidence of achlorhydria among the population living on a monotonous lacto-cereal diet than among the population living on a mixed diet. Even though Alvarez, Pilcher, Foley, Mayer and Osterberg (37) were unable to produce a change in gastric secretion in two normal persons by feeding a diet deficient in vitamin B, it is possible that a vitamin deficiency may further reduce gastric acidity in the malnourished cancerous patient with a chronic inflammatory change in the mucosa. This is not an impossible explanation in view of the above-cited experimental and clinical data and the actual occurrence in cancerous persons of an avitaminosis such as pellagra.

SUMMARY AND CONCLUSIONS

Gastric secretory activity before and after the development of cancer of the stomach has been studied in seventy-nine cases. The gastric secretory activity of the seventy-nine patients destined to develop cancer of the stomach was below normal before the development of cancer. After an interval of years averaging six, and after each patient had developed cancer of the stomach, the percentage of achlorhydria had increased from 38 to 64.6 per cent, while the mean concentration of free hydrochloric acid in the gastric contents of the remaining twenty-eight patients who retained free acid was little changed. The depression of gastric acidity in patients destined to develop carcinoma of the stomach is a progressive and selective process, appearing early in life and at all ages. The low secretory activity of the stomachs of patients with gastric cancer is present, for the most part, before the development of cancer. The loss of gastric acidity occurred in patients both with high and low concentrations of free acid but more frequently in cases in which the concentration of acid was low before the development of cancer. A further reduction of gastric acidity occurs after the development of cancer. Its frequency and importance are unknown. Theoretically, the low secretory activity of persons destined to develop carcinoma of the stomach may be present at birth (a developmental defect in the secretory mechanism), or it may occur after birth as the result of an abiotrophy of the acid secreting cells or as the result of inflammatory destruction of the gastric mucous membrane. The loss of gastric acidity in adult life excludes a developmental defect as the cause of the loss in a considerable number of cases, while the presence of marked, diffuse atrophic gastritis in almost all cases of achlorhydria and the absence of a marked diffuse atrophic gastritis in almost all cases in which there is free hydrochloric acid in the gastric contents, greatly favor chronic atrophic gastritis as an important cause. In fact, chronic atrophic gastritis appears to be the important cause. Chronic gastritis, as well as the tumor itself by its local and systemic effects, may be responsible for the depression of gastric secretion after the development of gastric cancer.

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DISCUSSION

DR. FRANKLIN HOLLANDER (New York, N. Y.): Dr. Comfort's very interesting paper brings to my mind a fundamental question regarding the physiology of hypoacidity, apart from its relation to the cancer problem. In order to account for the low acidities which are associated with carcinoma of the stomach, Dr. Comfort and his associates have suggested several alternative mechanisms. One of these is neutralization by an alkaline fluid from the gastric wall; another is a progressive diminution in the volume of acid secretion which is formed by the parietal cells. Now, there was a time, not so long ago, when we felt it necessary to differentiate between hypersecretion and hyperacidity. Today we no longer feel the need for this differentiation, for we now know that the acidity level at which the secretion is formed in the gastric glands is practically constant and that this constancy persists in spite of other physiological variations of considerable magnitude. As a result, any extensive change in acidity of the gastric contents has come to be considered as due to a corresponding change in the relative volume of parietal secretion which is poured into the gastric cavity. In short, instead of talking about hyper- or hypoacidities we now speak of hyper- or hyposecretion.

More recently, however, with an extension of our knowledge of the chemistry of the gastric juice, we have been confronted with another dichotomy of this kind; namely, where we have an apparent hypoacidity are we dealing with a diminished output of gastric juice, or, are we concerned with an increase in the extent of neutralization (and dilution) of the hydrochloric acid by some alkaline buffer-containing fluid? This fluid may be an actual secretion, a transudate, regurgitated duodenal juice, or something similar.

Now, unlike the earlier dichotomy, this one has not yet been resolved. At the present time very few investigations involving low acidity values are concerned with differentiating between a lowered volume of acid secretion and an increased volume of non-acid fluid. The reason for this situation is simply this: that as yet we have no chemical analytical method which will enable us to distinguish between the two. Thus, although we are fully aware of the problem we are rather at a loss as to how to investigate it. Dr. Comfort's paper presents this same dilemma; it offers these two possible mechanisms in connection with certain clinical manifestations of diminished acidity, but the authors have not coped with the problem which they raise. Sooner or later it must be faced, since it is concerned with a matter of fundamental physiological importance. In this particular case I would venture the suggestion that both factors are operating simultaneously, but that is only a guess.

At the present time at our laboratory in New York we are deeply interested in this very problem. In fact, one of our lines of research is intimately concerned with a method which can be used to measure both the volume of acid secretion and the extent of neutralization and dilution by non-acid secretion. I should like to ask Dr. Comfort whether any such differentiation is being attempted at the Mayo Clinic and whether any such laboratory method is available there at present.

DR. SIDNEY PORTIS (Chicago, Ill.): I should like to ask a question. In the second group of twenty-one cases what was the relationship between operability and achlorhydria?

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): One object of this study was to confirm or refute a somewhat sweeping generalization made several years ago by one of our distinguished British colleagues. On the basis of a few cases coming under his personal observation, apparently supported by a few others reported in the literature, this physician maintained that anacidity in the presence of gastric cancer preceded the onset of the disease, and that those having acid before the development of cancer would always retain it. He further argued that the precursor of the former type was a chronic gastritis, and of the latter a gastric ulcer, in the majority of cases.

Well, our own observations and convictions and the experience of some contemporaries would seriously question such conclusions, even before a critical study was undertaken. While freely open to conviction, I think we have definitely shown that in a certain percentage of the cases the onset and progress of gastric cancer results not only in a lowered concentration and secretion of hydrochloric acid but in an actual cessation or complete neutralization of it. As to the actual cause of such phenomena, this is still a moot point. In this connection I might add that I have also seen the smallest carcinomata actually discovered while examining patients for other conditions which were well within the normal size range of benign ulcer and yet there was a complete absence of hydrochloric acid refractory to histamine stimulation. It is also true that as the growth increases in size the depressing influence on gastric secretion is frequently observed. The factor, or factors, likely responsible for this phenomenon have been discussed.

The well known observations of Konjetzny and others, as well as recent histologic studies of our own resected material (Baker) do confirm the importance of gastritis, not only as a precursor of carcinoma, and which is in agreement with Hurst's observations, but as an important factor in the depression or cessation of gastric secretory function. But on the other hand, to maintain that gastric carcinoma associated with free hydrochloric acid has its origin in an antecedent gastric ulcer seems to us quite difficult of proof, even though it is true of a certain

number, perhaps not exceeding 10 or 15 per cent. Until we can make careful objective studies of individuals destined to have gastric cancer, the problem of precursors, aside from those already known, may go unsolved.

DR. ROBERT ELMAN (St. Louis, Mo.): A number of years ago while studying a series of cases with a test meal composed of 300 c.c. of five-tenths per cent hydrochloric acid, I had occasion to observe a number of patients with proved gastric carcinoma. In each instance there was much more rapid neutralization of this introduced acid than occurs in the normal, which indicates, it seems to me, that perhaps the anacidity in cancer of the stomach may be due to excessive neutralization of acid rather than to true hyposecretion.

DR. HENRY L. BOCKUS (Philadelphia, Pa.): I think this is a tremendously important consideration. I suppose it will be a good many years before anyone will have an opportunity to report a series of cases of this size, of cancer of the stomach that have been previously studied from the gastric secretory standpoint and for that reason alone it is tremendously important, but over and beyond that, it seems to me that it was about time that someone who has a wealth of material refuted the stand of Hurst, because if Dr. Hurst is right, then I suppose most of us sooner or later would assume that gastritis or achlorhydria, or achylia is the cause of cancer.

I can't even altogether agree with Dr. Eusterman in his statement that it has been proved that most cases with cancer of the stomach have a diffuse pangastritis. It has not been proved in many of the cases we have dissected in Philadelphia, not a diffuse pangastritis—a gastritis that is near the lesion, that is very true, but I, for one, do not feel there is enough experimental or pathological data at hand to support the contention that many cases of cancer are engrafted on a previous gastritis.

Another thought of a little interest, is that in our cases we rarely see a true achylia in cancer of the stomach. Many of our cases of cancer are achlorhydric but respond readily to histamine. I take it from Dr. Hurst's writings that he feels that people with constitutional achylia gastrica are predisposed to cancer of the stomach. I know of nothing, clinically or pathologically that bears out that statement, and I think for that reason the paper that Comfort, Butch and Eusterman have presented here is a very important one.

DR. MANDRED W. COMFORT (Rochester, Minn.): The number of cases in this series was too small to allow conclusions to be drawn regarding the relationship between operability and the degree of free acidity. Other work, such as that of the Eusterman and Bueermann, Comfort and Vanzant, show that the operability of the lesion decreases as the percentage of anacidity increases.

The relationship between the situation of the lesion and the degree of free acidity in this series was not studied. Doctor Vanzant and I studied this point statistically in a large number of cases of cancer of the stomach, and were unable to see that the situation of the lesion materially influenced the degree of free acidity.

Doctor Hollander has asked if any attempt has been made to distinguish between low gastric acidity owing to deficient secretion of hydrochloric acid and that owing to increased neutralization. No such distinction has been attempted in these cases. The degree of mean free acidity and the mean volume of gastric content obtained by continuous siphonage from the cancerous stomach after stimulation by histamine are lower than those obtained from the normal stomach. The combination of low volume and low acidity can best be explained by the secretion of a smaller volume of acid gastric juice. It is possible, of course, that the volume of neutralizing fluid is increased but in view of the low volume of mixed gastric content obtained, the increase in the volume of neutralizing and diluting fluid must necessarily be small. It is our belief that inflammation of the gastric mucosa, so frequently found in the cancerous stomach, plays an important causative rôle in the deficiency of the secretion of free hydrochloric acid.

The Psychobiological Approach to Gastro-Intestinal Disorders*

By

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SINCE the days of Hippocrates, much has been written in our medical literature about the study of the patient as a whole. [We have been admonished and taught by earnest and sincere clinicians that a diagnosis should not be made until all factors have been carefully considered and evaluated. In physical diagnosis, we are taught to investigate all of the systems carefully before writing a diagnostic summary and that such a summary should contain all of the findings indicating a variation from the normal functions, as well as historical data concerning previous illnesses, especially those of a familial or hereditary nature. In spite of all of this, and if a patient's study contains only this, we find that such a study of the patient is quite incomplete]. However, until quite recently, the study of the patient as a whole has been, as the late Dr. William A. White expressed it, chiefly "lip service." Furthermore it has been definitely shown that when a careful and complete physical examination is made, including all of the laboratory tests that are possible, the summary of such a study often reveals very little in the nature of pathological findings, yet the chief complaints of the patient or the complaint problems of the patient are of a nature to indicate a disturbance of function and that there is, after all, something wrong. Only recently have the psychosomatic aspects and the emotional causes of illness been recognized. These emotional factors may be the underlying cause of indigestion, sour stomach, eructations, pain in the epigastrium, loose bowel movements or constipation, together with headache and feelings of general malaise and discomfort and anxiety with more or less discouragement. The court of final appeals, namely, the X-ray examination, to be sure in many of these patients shows only slight variations from the normal, and usually not sufficient "sui generis" to account for the degree of discomfort of the patients. Yet the patient's symptoms persist and what is to be done? It is not only with this group of patients, where emotional factors or an underlying neurosis is followed by a train of symptoms and complaints closely simulating actual organic pathology of the intestinal tract, that we wish to call attention, but it is the possible rôle of such emotional mechanisms in the etiology of what may later prove to be definite peptic ulcer or ulcerative colitis or other organic conditions of the tract in the emotionally unstable person. Our responsibility as psychiatrists and internists, in relationship to the patients of this type, can be fulfilled only when we consider ourselves physicians and approach every patient with a broad and non-prejudicial point of view. Seeing before us, in each patient a psychobiological study, with the interrelated processes of the psychological, best expressed as emotional factors and responses, exerting their effects on the physiological processes of digestion, assimilation and metabolism, then we must look for the underlying cause of the emotional disturbances. This leads us to a study of the patient's social situation or environment in its broadest sense, an investigation of the psychological factors or a search for the totally integrated personality factors conditioned as they are by heredity or instinctual components, and environmental circumstances or the sociological factors. Such a study and total evaluation in present-day psychiatry or medicine is spoken of as the psychobiological approach and likewise as a genetic-dynamic evaluation of the patient.

Since 1930, when the writer began the psychiatric work in the Out-Patient Department of the Massachusetts General Hospital and formal psychiatric consultation work on the wards psychiatry in itself has changed and developed tremendously in that it is becoming closely integrated into all medical work, not only with us but in many of the leading medical centers of this country.

The late Dr. William A. White recently referred to two great achievements in psychiatry that have taken place during the past 25 years. First, the mental hygiene movement in this country; and second, the development of dynamic psychiatry or the psychoanalytical theories and principles. It would seem to the writer that there is a third of equal significance, and this is the integration of psychiatry into general medicine, not alone in the form of special psychiatric clinics in general medical centers or in the out-patient departments of general hospitals, but in the actual collaboration of psychiatrists with internists and surgeons on the wards.

From the writer's experience, it seems apparent that the greatest value rendered by psychiatrists in the general hospital lies in the opportunity of studying patients at the bedside in the medical wards along

*Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, June 7 and 8, 1937.
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with the internists and in some instances with the surgeon, or in the special clinics in the out-patient department, such as the diabetic, the arthritic, the medical, the thyroid, the cardiac, and, what seems most important to us, the gastro-intestinal clinic. Under these conditions, the psychiatrist acts as other consultants and evaluates the psychic and emotional factors in each given patient's study and adds to the completion of the consideration of the total clinical picture and aids in determining which cases should be studied primarily from a psychiatric point of view, there being many cases of course where the immediate medical and surgical problems take precedent beyond any doubt. On the other hand, there are many patients where we have found it was distinctly advantageous, if not necessary, that they should be studied by the internist, the surgeon, and the psychiatrist at the same time or concurrently.

In the gastro-intestinal clinic of the Massachusetts General Hospital, several internists and surgeons, the writer and a psychiatric research fellow constitute the staff. The psychiatrist frequently sits in with the internists or the surgeon during interviews to ascertain the relative importance of emotional factors in a given patient's study. Since the patient's formulation of his or her complaint problems and the patient's own description of symptoms often indicates not only ulcer or anything but ulcer, it indicates also the type of personality we are dealing with as Meyer expresses it the he or the she in the total situation, and many times factors of a social, domestic, economic, or psycho-sexual nature may be readily discerned as the patient's important trouble. Patients should usually be thoroughly examined physically, yet it may be unwise, in the best interests of the patient, especially in certain emotional types, to delve too extensively into special studies or to make special examinations merely to rule out pathological lesions. In many emotionally unstable patients, such procedures add further conflicts to an already overburdened and emotionally, if not mentally ill, patient and tend further to fix the idea of illness in a damaging way, especially where the emotional patterns may be in a formative stage and incapacity is sought as an escape mechanism. The psychobiological approach attempts an investigation and study of patients with gastro-intestinal complaints, proceeding from the "complaint problem" of the patient. The psychic factors are so frequently an outstanding part of the illness of the patient that such considerations of the relative presence or absence of organic pathology is not important in this new and combined study and consideration of gastro-enterological disorders. Then, of course, one not only has to deal with psychic and emotional factors as a primary cause of the disorder but with the psychic disturbances that are secondary to organic disease of the tract. It is on this latter group that I should like to place a special emphasis, since most of the patients seen by the writer in our clinic have or have had definite organic pathology—a definite ulcer or colitis, etc. These patients have been given the customary medical and, in some instances, surgical treatments; nevertheless their clinical progress, in so far as their clinical picture and symptomatology is concerned, still remains unsatisfactory. We have found in many patients that psychic factors, possibly instinctual in origin and manifested as a subtle complication of the personality, in addition to the above, must be dealt with before real clinical improvement can take place.

These patients are from the routine clinical and hospital practice and necessarily have comparatively few contacts with the psychiatrist. Yet the following patients serve to show how important and valuable a psychiatric study can be, even though it is superficial and the hours of psychotherapy are limited. Not only can there be a more complete evaluation of the patient from a psychosomatic standpoint, but the results of psychotherapy of a psychodynamic type, in conjunction with the medical regime of the internist and the surgical procedures and observations, aid materially in dealing more adequately with the patient as a whole, as well as with the specific patient's complaints which are, in most instances, found to be a complicated milieu of organic and physiological, psychic or emotional disturbances rather than such simply defined symptoms as pain, nausea, diarrhea, discomfort, or constipation. There is little need to stress the fact that, in spite of our interest and in spite of the increasingly psychodynamic emphasis in all medicine and research, we psychiatrists have yet little actual concrete knowledge of the mechanisms relating emotions and bodily changes, and we are still handicapped by the limited research methods in this field and the imperfect development of those who are working in a manner similar to ours.

The significance of the conditioned reflex (Pavlov and von Bergmann is well known). Even without a conditioned reflex the site of some previous somatic disease becomes readily the site of an organic neurosis. An hysterical individual, for example, develops swelling of the joints, having previously suffered from a rheumatic arthritis. The body has learned, as it were, the symptom. Furthermore the sense of well being remains decreased in a bodily part that has once been ill. This is the basis for the phenomenon of Hängenbleiben described by Heyer. The pain caused by somatic disease long outlasts the duration of actual organic disease.

This is illustrated by the following case study:

A. S., No. 8027, a married housewife, age 33, has been under care and treatment in the gastro-intestinal clinic for three years. Her symptoms were fairly typical of ulcerative colitis, and, because her symptoms became worse, she was admitted to the house for treatment Oc-

tober, 1936, when an ileostomy was performed and followed by colectomy. Following a normal and satisfactory convalescence from this operation, the patient was discharged from the house in December, 1936, to be followed in the out-patient clinic. She has been seen fairly frequently by the internist and surgeon, and her clinical course, as far as the symptoms of her colitis are concerned, has been entirely satisfactory. She does not, however, consider herself well and complains of nervousness and of queer feelings that are difficult for her to describe. She feels frightened and now still has feelings of discomfort in the abdomen which are not unlike those she had with her colitis. At times there still seems to be the pain that she previously experienced. This patient was seen by the psychiatrist several times before she entered the house for operation. That she is emotionally unstable is undeniable. The present emotional symptoms and residual pain-like experiences represent a conditioned reflex situation and the persistence of the symptoms caused by organic pathology even after the pathological lesions have been removed. This patient is fairly cooperative and simple explanations are grasped and in so far as possible accepted. She must be given, however, a substitute in the way of re-education and diversional interests to take the place of her actual pathological condition which previously preoccupied her. Psychotherapy and an intelligent medical regime will prevent this patient from becoming a helpless neurotic or a drug addict, since sedative drugs have been given all too frequently in the past for this particular type of pain, which persists or outlasts the duration of the actual organic disease. A symptom having its origin in organ symbolism may nevertheless become a conditioned reflex in its own right and then become activated through bodily processes without further psychic causation. Cardio-spasm may develop as a psychogenic organ symbol. Then the psychic cause drops out and the symptom remains as a response to the act of swallowing.

The following case of cardio-spasm illustrates the foregoing statement:

F. P., an American housewife, age 39, has been seen in the gastro-intestinal clinic since 1931. Her chief complaint is pain in the epigastrium, regurgitation of food, and malnutrition. In 1932, it was demonstrated that she had constriction in her esophagus. This was relieved by surgical interference with a cardio-plasty. Subsequently, however, her symptoms recurred, and her cardio-spasm has been relieved by the use of nitroglycerin. She has been quite dependent on nitroglycerin which has relieved the dysphagia, the cardio-spasm, and vomiting. At times, however, she has been able to go several days without her symptoms.

Because of the suspected emotional factors in this case, she was first seen by the psychiatrist in 1931. Her social history reveals that she is the mother of two sons. The older son, 17, is an epileptic, having frequent convulsive seizures. Her younger son of 13 is mentally retarded. Her husband is an electrician and earns a small salary. She is a woman of considerable intelligence and cultural background with a love for "the better things in life." She states quite frankly that she is making the best of life and refers to her husband as a very kind man. She has only part of the necessities and none of the luxuries of life. She has been interested in reading a better than average class of literature and has written poems and sonnets that have been published in magazines and papers and have afforded her a small income. She describes her husband further as a kindly, gentle, unromantic person. This patient's personality can be further characterized as an imaginative, romantic, and obviously unstable individual forced to live in a social atmosphere and at an economic level far below that which she desires. She has extreme apprehension and fear regarding the situation of her oldest son, and she is decidedly on the defensive and excuses the failures of her younger boy. Her sexual life is poorly adjusted, and she gains little satisfaction, although she has a strong desire. Sexual intercourse leaves her usually tense, apprehensive, unsatisfied, and is followed by fantastic dreams, obviously of the wish fulfillment type. Her cardio-spasm and physical symptoms are always intensified following intercourse and likewise following worry or following the epileptic seizures of her oldest boy and are frequent accompaniments of her depressive moods when her social and economic dissatisfaction looms vividly before her. Psychotherapy at times during the past two years has seemed to relieve the patient's symptoms. It was confidently expected by the writer that more intensive psychotherapy would cure this patient's cardio-spasm. In April, 1937, however, this patient's physical condition became actually so acute that it was felt she should have bougies passed. The esophagus was dilated, and the patient was seen at the same time not only by the internist but by the psychiatrist. During this procedure, the patient was emotionally tense and between the interviews had bad dreams, complained of a good deal of pain, and was generally worried. In spite of this however, she was able to eat and discontinued the use of nitroglycerin. During the past two years, this patient's weight has rarely been over 105 pounds. Since April, she has gained 10 pounds in weight, now weighing 115 pounds and is symptom free. It is interesting that she still has all the sensations that she had when she suffered her cardio-spasm, yet she does not vomit, but she seeks relief of these uncomfortable feelings as well as of other emotional symptoms. She will therefore be followed in the clinic.

The following patient, M. P., No. 34286, an American housewife, age 41, was referred from the clinic to the house January 1, 1936, because of symptoms of a severe colitis. X-ray examination and proctoscopy showed a typical ulcerative colitis. She had mucus and blood in her stools, had lost a great deal of weight with severe pain, and was in a highly emotional state. She remained in the house until February 25 and, under a medical regime, her symptoms improved. She has been followed in the clinic by the internists and the psychiatrist. This patient's emotional symptoms were unquestionably occasioned partly by the menopause, together with apprehensive feelings of inadequacy and insecurity, and exaggerated fatiguability, together with vaso-motor disturbances characteristic of the menopause. This patient's whole life was complicated by a husband who drank and a mother-in-law

who was somewhat interfering. A daughter, who was difficult to discipline and who was just arriving at puberty, created further conflicts in the patient's mind. Under a medical regime and with a reasonable amount of psychotherapy, this patient has passed through her menopause and has not had any symptoms of her colitis for nearly a year. She has been able to do her housework and at the present time is enjoying the best health that she has ever experienced in her life.

Case No. 4, N. S., an American housewife, age 36. This patient was first seen in the medical clinic where she was treated for symptoms of cardiac disease. It finally developed that she apparently had a normal heart, but she had symptoms referrable to her gastro-intestinal tract suggestive of an ulcer. She was seen in the gastro-intestinal clinic where a diagnosis of duodenal ulcer was made and confirmed by X-ray examination. In the clinic, she was referred to the psychiatrist who also recognized her extreme emotional instability. After considerable reluctance, she stated that she had been a patient in one of the state hospitals, the record from this hospital showed she was diagnosed as a manic-depressive psychosis of a mixed type, and reports further that she was in a state of euphoria, exaltation, depression, hypersuggestibility, psychomotor excitement, made suicidal and homicidal threats. This patient has been on the usual medical regime in our clinic, but the psychiatric factors seem equally important. Although this patient is free from any gross mental symptoms at the present time, it has been difficult to get this patient to cooperate with her diet and to take periods of rest, although she is perfectly frank in an exploration of her psychogenic background. Some of the important dynamic factors in this patient's life situation have been a disappointment in love and a pregnancy before marriage which resulted in an abortion. She, being a Catholic of the high Anglican faith and having married a man because he was kind enough to have assisted her with her abortion even though she had no love for him, created early in her married life severe conflicts. Although her early life was uneventful, her mother suffered from periodic attacks of manic-depressive psychosis. Her present marital existence, except for her extreme love and accentuated maternal attachment to her only child, a boy of 9, is exceedingly drab and prosaic. She has strong sex drive and receives no satisfaction from sexual relations with her husband. She has been tempted to indulge in extramarital intercourse, and there have been marked emotional upsets as a result of mental conflicts over this problem. She has none of the luxuries in life and, although she is quite an attractive woman, she feels thwarted and compelled to remain at home because of the lack of suitable clothing. Psychotherapy and an effort to secure some employment for this woman so that she has been able to earn money for proper clothing and a better understanding of her sex life on the part of her husband have already helped this patient. We have been able to help her rationalize her situation and to give her some interests in life and some hopes for her future so that her mood swings are less marked and her ulcer symptoms have almost completely disappeared.

Time does not permit of a discussion of the interesting psychiatric factors and the psychological mechanisms and their probable relationship to the clinical symptoms in these cases. It is obvious that disappointments and frustrations have led to emotional conflicts which, in turn, have complicated the normal physiological functions of these patients, with a special reference to disorders of the gastro-intestinal tract. Psychotherapy in these patients has been directed toward better rationalizations and sublimations of these psychological disturbances. That this has been profitable to the patients is undeniable in view of their improved clinical progress.

This paper, therefore, reports an attempt to approach the individual clinical problems with our available methodology and technique. It is hoped that from such a clinical study carried over a sufficient period of time, we may obtain a more complete orientation and understanding in the psycho-somatic field in so far as disorders of the gastro-intestinal tract are concerned. Clinical studies of the above nature can be aided by more comparative physiological and psychiatric studies of the emotions in humans. Experimental studies on animals, as well as on humans, conducted by the usual scientific physiologists, without the background and study of the total personality from a psychobiological point of view, can help us very little toward the solution of the usual patient's problems which involve so high a number of interrelated variables.

Thus the value of a psychiatric study of patients with gastro-enterological disorders may be twofold, first to gain more knowledge of the relationships between emotional disturbances and the actual organic pathological conditions, which will lead us to a better understanding of this group of psychosomatic disorders, and secondly, to give our patients more intelligent and satisfactory treatment on the basis of the logico-experimental evidence gained through such a psychobiological approach. To this extent, the psychiatrist may have valuable suggestions in a considerable number of the patients studied and treated in the gastro-intestinal clinic.

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DISCUSSION

DR. ALBERT J. SULLIVAN (New Haven, Conn.): At Yale for the past three years we have followed the example of the Massachusetts General Hospital and we have a psychintrist associated with the Gastro-Intestinal Clinic. The result of this association has been that we have paid more attention to studying the person who has the disease, in contradistinction to the disease that the patient presents.

We are particularly interested up there in the way that patients experience things. Dr. Kahn, of course, who is chief of the Psychiatric Clinic, is noted for his studies in personality.

It is frequently stated that financial and sexual difficulties, for example, can have very little to do with the onset of a peptic ulcer or ulcerative colitis, because, after all, most of us at some time of other have financial worries or sexual difficulties, and very few of us develop ulcerative colitis or a peptic ulcer. Individuals differ in their ways of experiencing things. There are an infinite number of possible combinations of personality types. We know, for example, that under financial worries or sexual difficulties one person may become an alcoholic, another person may commit suicide, a third person may develop a major psychosis, and what we feel, what our studies tend to show, is that certain personality types, given these rather common emotional difficulties, may develop certain specific gastro-intestinal reactions. They may react to these difficulties by the development, or at least the exacerbation of, a peptic ulcer or of ulcerative colitis.

What we hope is that the psychiatrist, by the careful study of a reasonable number of cases of peptic ulcer or ulcerative colitis, by complete psychiatric studies—these, of course, take a great deal of time—will be able to define for us the personality types which tend to develop a specific gastro-intestinal disease and aid us in finding out and anticipating the types of emotional reactions which upset these particular people.

So far we feel that as far as ulcerative colitis and peptic ulcer are concerned, we have definite leads towards both those problems; first, the type of patients who develop the disease, their personality traits; and, secondly, the types of emotional reactions which get them into difficulties.

One could, I suppose, draw a parallel with the allergic individual. After all, passive transfer tests have shown that all of us absorb unaltered protein from the gastro-intestinal tract, but we do not all develop allergy. Of those who are allergic or sensitized, or whatever it is, we have words for it but we still don't understand it—of those who are allergic, some develop asthma, some develop skin disease, some develop hay fever, some develop gastro-intestinal reactions; and I feel that the parallel can hold for certain specific gastro-intestinal diseases, that there are specific personality types that tend to develop specific gastro-intestinal diseases, and that certain emotional reactions, certain emotional problems to which these individuals are sensitive, produce clinical exacerbations.

DR. KENNETH J. TILLOTSON (Waverley, Mass.) (closing the discussion): Mr. President, I wish to thank the discussant. I think there is little danger in trying to delineate special personality types on the basis of our present knowledge in connection with these medical disorders. It is an admirable effort and, of course, everyone recognizes in Dr. Kahn one of the leaders in the study of personality types, particularly of the constitutional psychopathic reactions.

In working with the alcoholic problems, which form one of our researches, we have come to the conclusion—we were speaking of alcohol as secondary, as a defense mechanism, and as secondary to various other situations, and we tried to find out what type of personalities drank, and we came to the conclusion, which may be a bit far-fetched, that real alcoholism is in itself a disease, and the personality of the alcoholic is therefore part of a clinical entity just the same as some other psychoses; to be sure this statement is subject to considerable debate. Our efforts have not been so much of a classificatory nature. We have attempted to find out what the emotional responses produced, and we have been working especially to give the patient more relief through getting a better understanding of the emotional factors in each clinical study, and not going perhaps quite so far as Dr. Sullivan and the group at Yale in the line of studying the personality.

It is an admirable effort and certainly one could not criticize such a scientific point of view as that of Dr. Sullivan and his colleagues.

DEMONSTRATION

DR. V. C. ROWLAND (Cleveland, Ohio): The whole point is that this is a very simple, quarter-inch, collapsible tube introduced through the nose, with a silkworm gut, and it is not irritating to the nose and may stay all week without stirring up much reaction and, being collapsible, it does not permit of any regurgitation. The drip proceeds with regularity, without any change. So far as I know, no one is using the collapsible tube, and it is worth looking at.

The demonstration in the adjoining room by Dr. Woldman consists in the passing of a new collapsible tube used in connection with the aluminum hydroxide drip. The tube is a simple, quarter-inch, collapsible soft rubber tube such as is used as a covering for cigarette drains. A stylet of silkworm gut is used to give it sufficient rigidity to be passed. After lubricating with mineral oil it is more easily passed than the semi-rigid nasal tubes. It is not irritating to the nose and may stay in all week without stirring up much local reaction. Furthermore, being collapsible it acts as a valve and prevents regurgitation due to straining or restlessness on the part of the patient. The aluminum hydroxide drip proceeds with perfect regularity despite variation in intra-gastric pressure. So far as I know, no one is using a collapsible stomach tube, yet it could be used for prolonged intra-gastric feedings of any sort with much more ease and comfort than with the rigid tube.

The aluminum hydroxide drip apparatus is on demonstration in the Scientific Exhibit at the A. M. A. Meeting.

Book Reviews

Dextrose Therapy in Everyday Practice. By E. Martin. New York, Paul B. Hoeber, Inc. and Harper and Brothers, 1937, 451 pp.

THIS is an attractively written and helpful volume reviewing the enormous literature on the use of dextrose in medicine. One does not realize until one looks through this book how useful dextrose is in scores of conditions. It will be a most useful book for the hospital resident who is constantly having to give intravenous and other types of injections containing glucose. There are a number of good illustrations showing the technic of administering these solutions, and there is an excellent index. The book is attractively printed.

W. C. Alvarez, Rochester, Minn.

Clinical Reviews of the Pittsburgh Diagnostic Clinic. Edited by H. M. Margolis. New York, Paul B. Hoeber and Harper and Brothers, 1937, 552 pp.

THIS volume is made up of some forty-eight articles on various phases of internal medicine, written by members of the Pittsburgh Diagnostic Clinic. Many of these articles summarize the experience of the clinic over several years. The volume is interesting and very readable, and will be a useful addition to the library of all those physicians who want to keep up-to-date. A helpful feature at the end of each chapter is a list of from ten to fifty articles suitable for further reading. These titles seem to be well chosen. There are two good indexes. Dr. Margolis is to be congratulated on a difficult job well done.

W. C. Alvarez, Rochester, Minn.

Pathology. By E. B. Krumbaar. New York, Paul B. Hoeber, Inc. and Harper and Brothers, 1937, 206 pp.

THIS is one of the most interesting of a series of excellent small monographs, each on some phase of medical history. Every physician who wishes to be educated must know something of the development of pathology and the theory of disease. It is hard to believe that modern scientific pathology did not come into being until Morgagni published his book in 1761. Only then did a man cast loose entirely from the ancient ideas of "humors" and only then was a book written in which conceptions of pathology were based only on what was found at the autopsy table. The book is well written. There are a number of interesting photographs, and at the end there is a splendid list of what Dr. Krumbaar calls "pathologic milestones." All in all, every student of medical history will want to own a copy of this delightful little volume.

W. C. Alvarez, Rochester, Minn.

Pathophysiology of Hunger Pains. Collected papers from the Medical University Clinic B. By Oline Christensen. Edited by Knud Faber. Series II, Volume 3, 1931.

THIS monograph of 170 pages is based on an extensive study of sixty-six cases. The author concludes that typical hunger pains are associated with vigorous contractions of the empty or nearly empty stomach. He admits, however, that often when the contractions are painful they are not more vigorous than normal.

Furthermore, when, as often happens, the contractions are painful on certain days and at certain hours and are painless on other days and at other hours, the difference cannot usually be accounted for by differences in the depth of the peristaltic waves.

When the pains are relieved by the taking of food, this seems to be due to the fact that the contractions become less forceful. The marked efficiency of an egg-milk mixture in giving relief from pain seems to be associated with the tendency of this particular food to quiet peristalsis.

No relation could be found between the tendency of certain vigorous contractions to produce pain and the degree of acidity of the gastric content at the time. The author suspects that there is a relation between the tendency for contractions to produce pain and the presence of gastritis in the region of the pars pylorica.

W. C. Alvarez, Rochester, Minn.

The International Congresses at Paris and Vichy

By

B. B. VINCENT LYON, M.D.

PHILADELPHIA, PENNSYLVANIA

The International Society of Gastro-Enterology was promoted by Dr. Georges Bróhee of Belgium, in 1934, and the First Congress was held in Brussels in July, 1935, under the Presidency of Dr. Jan Schoemaker of Holland. It was a success. Dr. Franklin A. White of Boston, acted as the "unofficial observer" of the American Gastro-Enterological Association at this first meeting and was one of the American signers of the Constitution of this new International Society.

The Second Congress was held in Paris on September 13, 14 and 15, 1937, in The Faculte de Medecine of the University of Paris, under the Presidency of Professor Pierre Duval, the famous French surgeon, and under the continued Secretary-Generalship of the able Dr. Brohee. In the opinion of the reporter—who was appointed by Dr. Ralph Brown of Chicago, President of the A. G. E. A. to act as its unofficial observer—this Second Congress was again such a success as to warrant much more serious attention and a much larger attendance on the part of members of this Association.

The two subjects discussed were

"The Early Diagnosis of Cancer of the Stomach" and "Acute and Chronic Obstruction of the Small Intestine." There were in attendance about 500 doctors representing 33 countries. To the French and the Germans went the honor of presenting the "major reports" of the first subject. Each speaker was allowed 20 minutes. The Program was as follows:

Rapports francais:

Diagnostic clinique et serologique: MM. le Prof. Paul Carnot et Dr. Caroli. Le radiodiagnostic: M. le Dr. Rene A. Gutmann. Le diagnostic gastroscopique: M. le Dr. Francois Moutier. Le diagnostic gastro-photographique: MM. le Prof. agr. Carin et Dr. Bernay. Le diagnostic chimique: MM. le Prof. Marcel Labbe et Dr. F. Nepveux. Le diagnostic histopathologique: M. le Dr. Ivan Bertrand. Le diagnostic chirurgical: MM. les Drs. Gatellier et Charrier. Conclusions generales des rapports francais: MM. les Prof. Pierre Duval et A. Gosset.

Rapports allemands:

Interne Medizin: Herr Prof. G. Katsch. Radiologie: Herr. Priv. Doz. Robert Prevot. Gastroskopie und gastroskopische Photographie: Herr Prof. N. Henning. Chemische Diagnostik: Herr Prof. Max Buerger. Pathologische Anatomie: Herr Prof. Staemmler. Chirurgie: Herr Prof. Sauerbruch. Conclusions generales des rapports allemands: M. le Prof. G. E. Konjetzny.

Both the French and German presentations were a distinct credit to their respective countries. This reporter was impressed with the grasp each speaker had of his individual topic and the able manner with which he presented his subject matter without using prepared manuscript but talking informally, reinforced at times by an abstract of "hand notes." At the conclusion of the major reports the program listed 53 official discussions of 5 minutes each in which representatives from 19 countries were to take part. Among the doctors from America the following were on the program to discuss the first subject:

R. Schindler, Anthony Bassler, Wm. C. Jacobson, Max Einhorn, Herman I. Goldstein, Roy Upham, Henry Rafsky, Samuel Weiss, H. M. Eberhard, Ben Asher, Reuben Finkelstein, S. W. Johnson, Edw. Kellogg, De Witt Stetten, M. Kraemer, A. L. Levin, D. N. Silverman.

Unfortunately there were a number of absentees. This reporter was given the opportunity of discussing the first subject in the place assigned to Ben Asher of Jersey City. From Great Britain the following doctors discussed the first subject:

Sir Arthur Hurst of London

A. Justras of Montreal

The second subject occupied the third day's Program. The 6 major reports on "Acute and Chronic Obstruction of the Small Intestine" were, in order presented, as follows:

Clinique Medicale: M. le Prof. Heliodoro Mogena (Espagne).

Chirurgie: M. le Prof. Sir D. Wilkie (Ecosse).

Physiopathologie: M. le Dr. Jean Bottin (Belgique).

Radiologie: M. le Dr. Krynski (Pologne).

Anatomo-pathologie: M. le Prof. Cagnetto (Italie).

Biochimie: M. le Prof. Felsen (U. S. A.).

The discussions were to have been participated in by 32 speakers from 14 countries as listed on the Program but again there were a number of absentees. The American discussors present included Max Thorek of Chicago; Max Einhorn, Roy Upham, Henry Rafsky and Anthony Bassler of New York; Hyman Goldstein of Camden and J. A. Ward of Birmingham, Ala.

The 6 official languages were French, German, Spanish, Portugese, Russian and English. To this reporter it appeared that approximately 50-60% of all papers and discussions were presented in French; 20-25% in German and the balance divided among the



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other 4 official languages. The Americans and the British were at a distinct disadvantage because of their linguistic deficiencies.

The Programs were run off with unusual precision and celerity, in view of the large number of papers and discussions. If a speaker was not present or not ready when his name was called the Chairman passed him over and proceeded to the next speaker with complete impartiality. There was no discussion from the floor.

Compared to American Medical Meetings of national importance, the Commercial Exhibits at the Paris Conference were very meager, were not well "ballyhooed" and were not well attended—save one. Comments were made by both the American and British delegates on the relatively large number of French exhibitors dealing in formidable looking apparatus for colonic irrigation. It seems to be more popular on the Continent of Europe than elsewhere. In fact you could, if you chose, have your colon "laundered" while you waited. The most popular exhibit was one displaying and dispensing a special brand of champagne—a very excellent champagne. But no one abused this hospitality.

After the Monday afternoon session was concluded a reception was held at the Hôtel de Ville where the Mayor of Paris and other dignitaries made the customary speeches of welcome and the customary group photographs were taken. Among other entertainments, the banquet on Wednesday night held at the Hôtel Lutetia on the Left Bank, was most impressive, dignified and formal, and Paris lived up to its reputation for food and wine. Pierre Duval was toastmaster and called upon representatives from a number of countries for short speeches. For the most part these were well prepared and delivered. Sir Arthur Hurst spoke for Great Britain and Dr. Anthony Bassler in his capacity as President of the U. S. membership represented the United States. This dinner was attended by more than 700, including guests. This concluded the Second Congress of the International Society of Gastro-Enterology.

On September 14, 15 and 16 another International Conference was held at Vichy under the Presidency of Professor Maurice Loeper, the famous French internist, and the able Secretary-Generalship of Docteur J. Aimard. At this Congress over 900 doctors from 60 countries, as well as their wives and members of their family were guests of the French Government, which owns the Vichy Spa, famous for its waters and baths. Most excellent hotel accommodation, as well as lavish entertainment, was provided. A special train to Vichy and back to Paris carried a large number of delegates and guests.

"Insufficiencies of the Liver" was the only subject discussed. To the uninitiated it may seem amazing that 23 major papers and 135 discussions could be devoted to this one topic. This is a testimonial to the great margin of reserve and the great power of reparation that the liver possesses. Many other organs would not have survived so much attention.

The first afternoon was devoted to the formality of Registration, followed by a special concert at the Salle du Theatre du Grand Casino, and a reception by the Mayor of Vichy and representatives of the Government where welcoming speeches and the customary photographs were made. One dined at one's hotel and at 10 o'clock a Soiree de Bienvenue was held in the Salons du Grand Casino with dancing and an elaborate supper.

Save for an hour's motor bus ride at noon of the 17th, giving the delegates and guests a too brief view of beautiful



Intestinal Toxemia

Modern eating habits often lead to the loss of normal selectivity of the intestinal mucosa with consequent absorption of protein substance not prepared for use in the body. The liver becomes overtaxed and protein sensitization—sometimes called intestinal toxemia or autointoxication—results.

Along with symptomatic treatment for constipation, diarrhea, and other symptoms which invariably accompany such a condition, the use of Soricin has been found to be of definite value. Soricin (sodium ricinoleate) possesses marked detoxifying properties and relieves the symptoms of toxic absorption.

The suggested use of Soricin as an intestinal detoxifying agent is based on extensive clinical studies. The value of this compound has been demonstrated in the treatment of intestinal toxemia, non-ulcerative colitis, allergic diarrhea, and "irritable colon."

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Vichy, its bathing pavilions and its bottling works, all of Friday and in addition Saturday morning was devoted to the 23 major reports and Saturday afternoon was devoted to the 135 five minute discussions listed on the Program. To facilitate official handling of the latter, the discussions were subdivided into three divisions: Biology, Medicine and Therapeutics. Each was held in a separate hall with adequate seating arrangement and under responsible Chairmanship, and the delegates and members wandered in and out to listen to such speakers as they might wish to hear.

The Program of the major reports of 20 minutes each was as follows:

Biologie

L'exploration fonctionnelle de l'insuffisance hepatique, par K. Glaessner (Vienne).

L'insuffisance hepatique pigmentaire, par M. R. Castex et A. Lopez Garcia (Buenos Aires).

La fonction soufree du foie, par Leon Binet (Paris).

La peau et le foie, par E. Urbach (Vienne).

Le foie et les glandes endocrines, par C. I. Parhon (Bucarest).

Liver insufficiency in malaria, par N. Hamilton Fairley (Londres).

Medicine

Les gros foies de l'enfance, par R. Debre, E. Gilbrin et G. Semelaigne (Paris).

Les oedemes des hepatiques:

Etude clinique. Facteurs extra-hepatiques de production, par J. Olmer (Marsaille).

Etude chimique des oedemes hepatiques, par A. Lemaire, A. Varay (Paris).

Les relations du foie et de la nutrition avec considerations speciales du systeme nerveux:

Physiologie experimentale, par A. Lathan Crandall, Jr., M.D., Andrew C. Ivy, M.D. (Chicago).

Pathologie clinique du foie, par W. Norman Elton, M.D. (Reading).

Maladies et desordres cliniques, par Anthony Bassler, M.D. (New York).

Bibliographie avec references, speciales sur la degenerescence hepatolenticulaire progressive, les effets des toxines, l'hemachromatose, les lipoides, etc., par Hyman I. Goldstein, M.D. (Camden).

Syndromes hepatiques neurogenes et neuro-endocriniens, par N. Pende (Rome) et M. Bufano (Sassari).

Les insuffisances circulatoires du foie, par M. Villaret, L. Justin-Besancon, R. Cachera et R. Fauvert (Paris).

Therapeutique

L'insuffisance cellulaire du foie et ses indications therapeutiques, par R. de Grailly (Bordeaux).

La medication hepatique dans les accidents d'intolerance, par M. Brule et J. Cottet (Paris).

Le pronostic de la crise operatoire par l'examen des fonctions hepatiques, par Pierre Duval, J. Gatellier, J.-C Roux et R. Goiffon (Paris).

L'insuffisance hepatique pre et postoperatoire et son traitement preventif et curatif, par B. O. Pribram (Berlin).

Le regime alimentaire dans la reparation du foie malade, par F. Gallart-Mones (Barcelone).

La therapeutique hydrominerale de l'insuffisance hepatique, par M. Piery et M. Milhaud (Lyon).

These reports, in whatever language of presentation, were abstracted in the other five official languages and paper-bound in a "Transactions" which was put in the possession of every delegate and member on his registration. Of the 23 major reports, eighteen were delivered in French, three in English. Again this reporter is enthusiastic regarding the presentation by our Continental Confreres. The major reports



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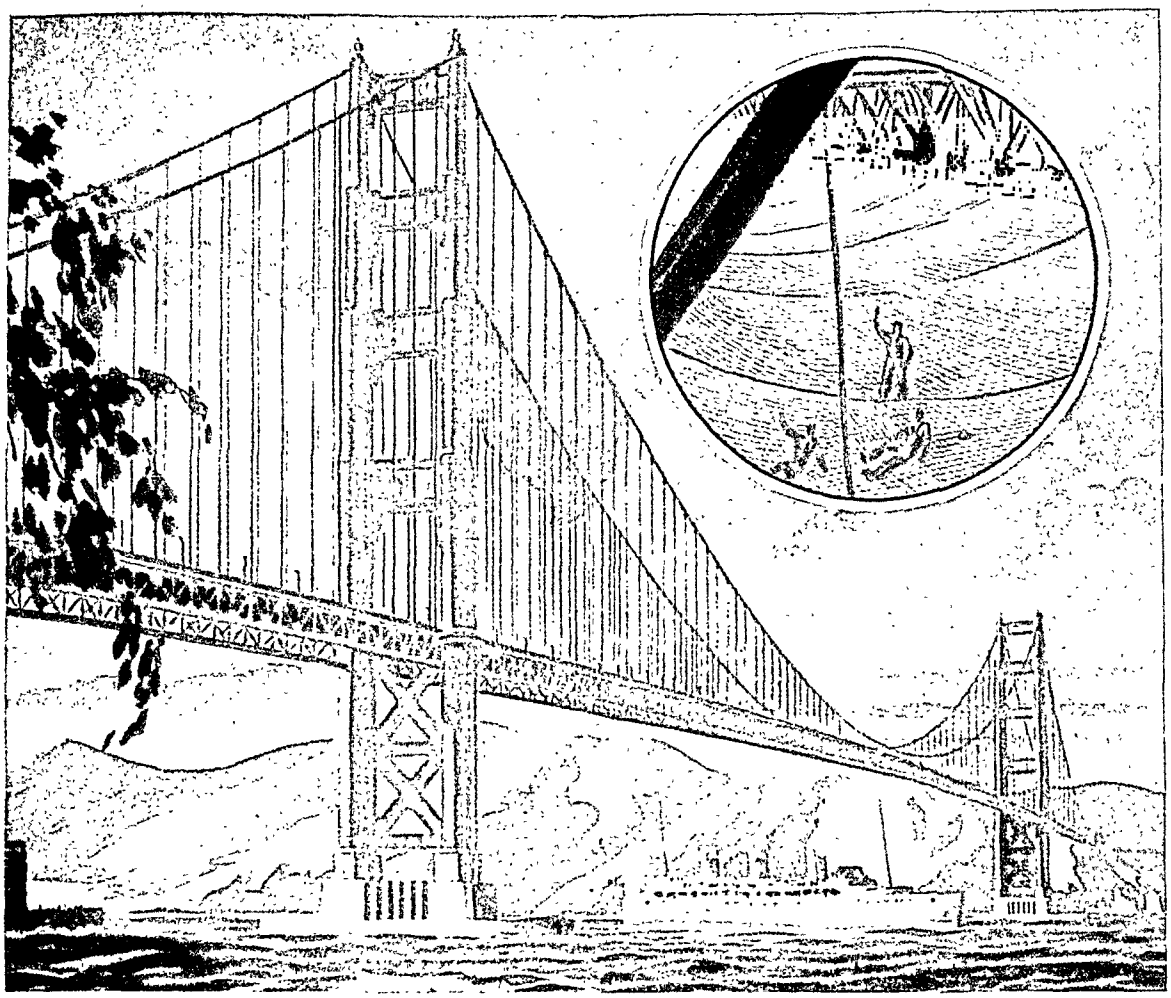
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of the American representatives, by comparison, were less able and less dignified. Drs. Crandall, Ivy and Elton were not present.

Among the approximately twenty Americans attending the Paris Conference this reporter noted the following members of the A. G. E. A.: Einhorn, Freeman, Felsen, Rafsky and Lyon. Of the 28 registered members at the Vichy Congress, the following fourteen were not in attendance: G. H. Whipple of Rochester (N. Y.); Ivy and Crandall of Chicago; A. A. Aaron of Buffalo; W. G. Morgan of Washington; Elton of Reading; Bishop and Stetten of New York; Rehfuss, Swalm, Eberhard and Mary Spears of Philadelphia; Silverman of New Orleans; F. A. White of Boston. Those present included Einhorn, Bassler, Upham, Twiss, Weiss, Rafsky, Lutz, Jacobson and Felsen of New York; Goldstein of Camden; Thorek of Chicago; Ward of Birmingham (Ala.); Sexton of Washington; Lyon of Philadelphia.

The most frequent question asked this reporter by delegates or members from other countries at both Congresses was "Why are there so few of the better known men in gastro-enterology in the United States in attendance? Where is so and so?" This reporter was unable to reply except to say that he hoped we would make a better showing in London in 1940.

On Friday night there was given in the opera house of the Grand Casino, one act from 3 operas, and two ballets, with leading roles taken by members of the casts of the Paris and Boulogne Opera Companies. On Saturday night an elaborate dinner was faultlessly served to over 1800 persons. Prof. Loeper, the toastmaster, called upon delegates from a number of countries for short speeches. Dr. Bassler again represented the United States.

This reporter believes that these International Meetings are very well worth while, promoting international amity as well as serving the excellent purpose of bringing together outstanding men from all over the world who are interested in a common topic. He believes that in the future those similarly interested in the U. S. A. should take a larger cognizance and a more active participation in future meetings.

The Third Congress of the International Society of Gastro-enterology was awarded to England. It will be held in London in 1940 under the Presidency of Sir Arthur Hurst.



Gastro-Intestinal Toxemias

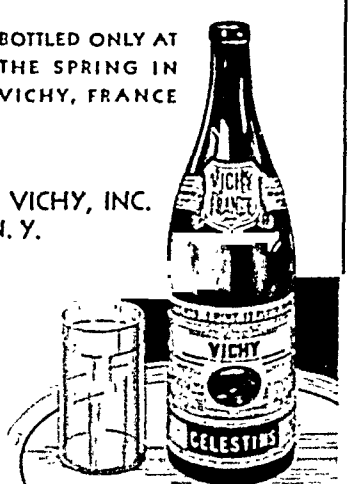
BECAUSE of its antacid properties, Vichy Celestins has been found useful for gastro-intestinal toxemias, particularly those of the fermentative type. In disturbances due to overeating, faulty diet or alcoholism, Vichy Celestins also has a marked corrective influence.

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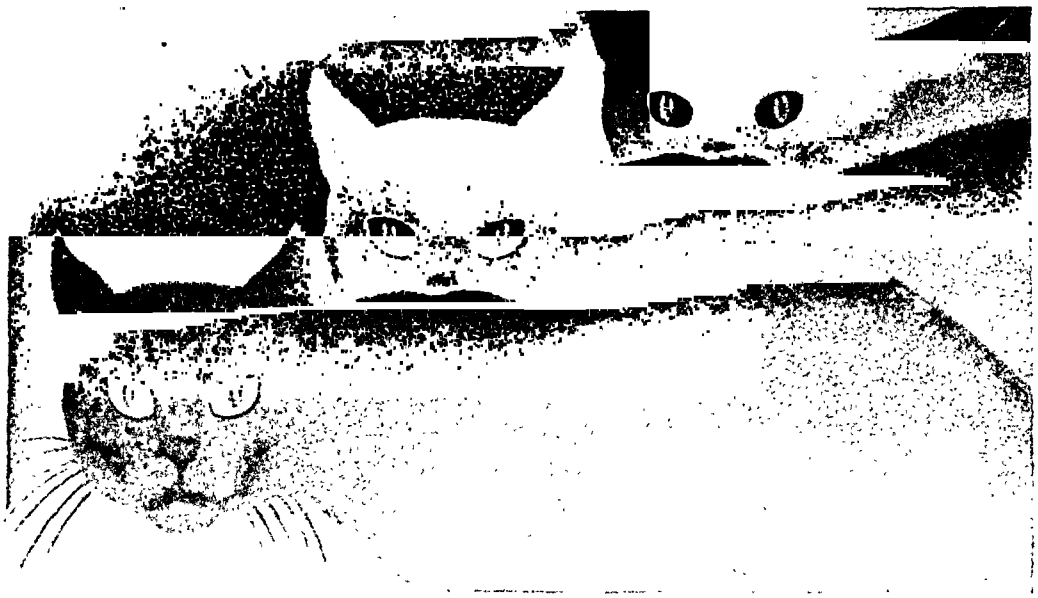
Abstracts

KOEPCKE, G. M.

Vitamins and Infections of the Eye, Nose, Throat and Sinuses. Lancet, Oct., 1937.

Four considerations now operate to foster the use of vitamins in otolaryngological practice, thinks G. M. Koepcke, M.D., Minneapolis. They are: (1) sounder, better work by investigators, (2) the visual photometer for vitamin A deficiency, (3) urinalysis and the capillary fragility test for vitamin C, and (4) to a lesser degree, the heart rate test for vitamin B.

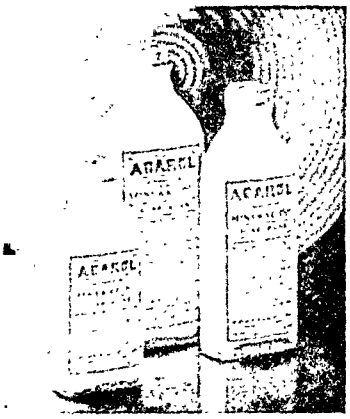
Vitamin deficiencies, Koepcke holds,



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To the physician who has tried mineral oil emulsions in the treatment of constipation—who has experienced disappointments of uncertain quality—who is now ready to try the sound logic and common sense of the principle that has brought distinction to Agarol—we extend this cordial invitation: "TRY AGAROL."

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are now all but established as causative factors in respiratory infections, while infections of the nose, throat and sinuses, must be considered in the light of avitaminoses. Though vitamins must not be regarded as "cure-alls"; nevertheless, they form a useful and necessary adjunct to other treatments and preventive measures. Bircher-Benner, for instance, declares that neither prophylaxis nor therapeutics will be wholly successful if there is a vitamin deficiency.

Lowered resistance is probably due to avitaminosis A and C. Avitaminosis A substitutes stratified keratinizing epithelium for normal epithelium in the respiratory tract; and Mackie believes infections of the eyes, tonsils, sinuses, buccal and lingual mucosa, and the skin, are due to avitaminosis A. Glands of internal secretion, particularly, seem dependent on vitamin A.

Tislowitz has treated diphtheria circulatory weakness with the adrenal cortical extract.

Treatment: The nutritional type of corneal ulcers respond very well to vitamin therapy. There is pain, scratching and soreness of the eye; small punctuate areas of ulceration are seen near the limbus. These coalesce after a few days, and corneal destruction progresses rapidly. Balanced combinations of vitamins reinforced by additional vitamins A and B stimulate healing and ulceration ceases.

Congenital cataract likewise yields to vitamin treatment if it is well fortified with vitamins A and C.

The convalescent period following severe acute inflammation is shortened if vitamin therapy is used; while herpes zoster ophthalmia should be treated with vitamin B_1.

If a patient complains of sensitivity to light, Koepcke recommends administration of vitamin A for several weeks, saying that he, himself, is usually able to estimate the amount required from his own clinical observations.

In sphenopalatine neurosis, the extreme pain and discomfort are speedily eased by administration of vitamin B_1.

Acute sinusitis, Koepcke advises, responds well to vitamin A plus combined concentrates; but the vitamins merely augment the routine treatment. The period needed to establish immunity to the predominating organism in the infection is much shortened, allowing quicker surgical intervention with less danger of extension of infection. The healing period is "surprisingly short." The vitamin A and concentrate must be given in large doses.

In general, Koepcke concludes, vitamins may be regarded as food for the endocrines, as good preoperative strengtheners of systemic resistance, and excellent curative agents in the conditions cited above. Surgical intervention is, of course, resorted to where indicated.

KRUSE, FRED H.

The Complications of Peptic Ulcer and Their Treatment. J. A. M. A., Vol. 109, pp. 869-874, Sept. 11, 1937.

The complications of peptic ulcer are intimately related and a brief consideration of their nature and treatment is of value. The most common ones are intractability, hemorrhage, alkalosis, obstruction, hypersecretion and perforation.

Intractable ulcers are those which do not respond to medical treatment. If, after foci of infection have been removed and nervous manifestations have been overcome, the ulcer does not respond, surgical intervention is the treatment required.

A bleeding ulcer usually is recognized by the appearance of gross hema-



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For rapid relief in the treatment of hyperchlorhydria and peptic ulcer without harmful systemic effects. Tri-Calsate causes no rebound in acidity, no alkalization of stomach contents. The buffering effect of its end salts protects against a harmful alkalosis, thus eliminating a major disadvantage of the alkaline antacids.

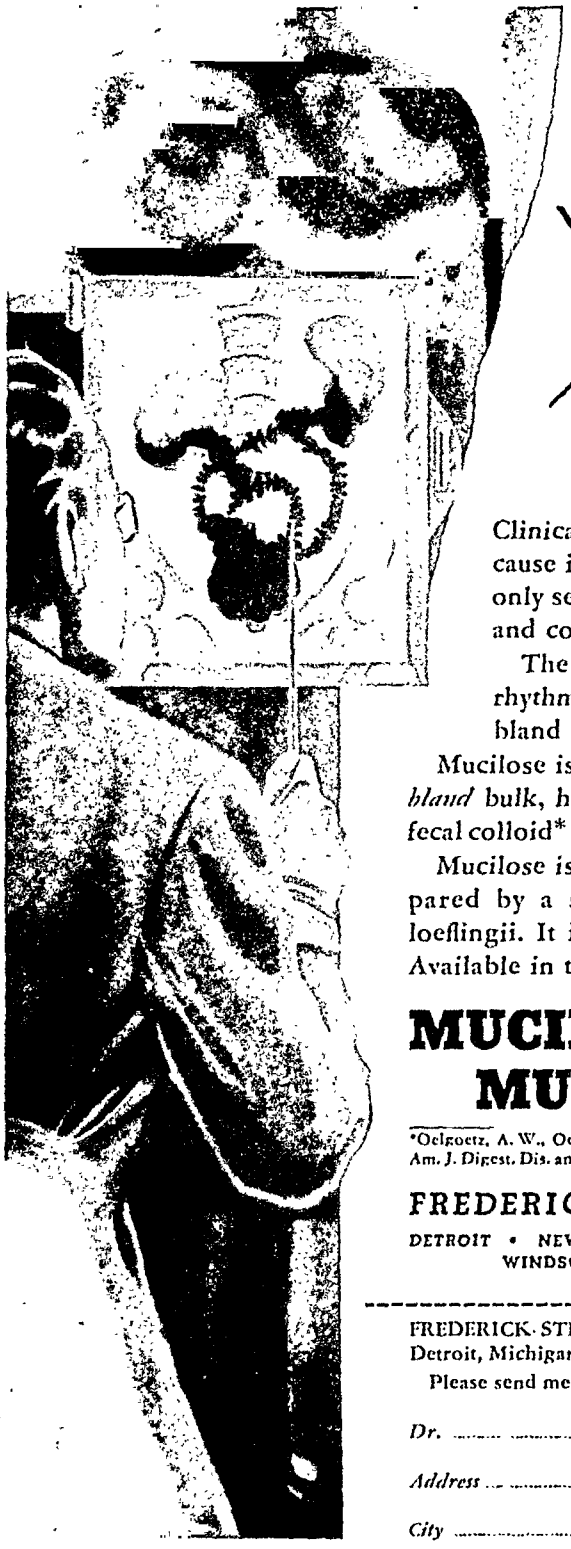
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*Oelgoetz, A. W., Oelgoetz, P. A. and Wittekind, J., Studies in Bowel Drainage, Am. J. Digest. Dis. and Nutrition 3:549, (October) 1936.

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temesis, or melena, or both. It is accompanied by the usual symptoms of severe blood loss. The treatment in the early stages is medical. It should consist of rest in bed with enough morphine to keep the patient quiet. Fluids should be given intravenously, subcutaneously and per rectum. The patient should be starved for at least 48 hours. The author believes that gastric lavage is beneficial when there is evidence of remnants of food or blood. The blood pressure, hemoglobin and red blood count should be carefully watched. Small transfusions are often of value. The patient should be alkalinized. If the patient does not respond to this treatment, surgical intervention will be necessary.

Alkalosis is due to obstruction, vomiting, renal disease, hemorrhage, low salt intake, excessive perspiration, hepatic disease and excessive doses of alkalies. It is characterized by anorexia, depression, distaste for food, irritability, headache, vertigo, timitus, nausea, vomiting, aching joints, pruritus, apathy, drowsiness and coma. Laboratory examination reveals a high nonprotein nitrogen, urea nitrogen, CO_2 of plasma and serum sulfate, while the blood chlorides and the sulfate clearance are normal. The urine will show albumin and casts, and the phenolsulphonphthalein test will be low.

The author's treatment is as follows:

1. Discontinue alkalis.
2. Give N. saline by hypodermoclysis and ten per cent dextrose intravenously.
3. No food or fluid is given by mouth.
4. Stomach lavage.
5. Ammonium chloride 300 c.c. of two per cent solution rectally or ten to twelve gms. by mouth.
6. Feed in three or four days.
7. Use of only neutral or insoluble alkalis in the presence of even a slight degree of renal disease.

Obstruction may be due to pylorospasm, edema and inflammation of the pylorus, or pyloric fibrosis and hypertrophy. It is characterized by increased pain, vomiting, dilatation, distress and emaciation. The treatment is a return to the first part of the ulcer regime. If this is not effective, surgical intervention will be necessary.

Hypersecretion usually accompanies obstruction and should be managed accordingly.

Perforated peptic ulcers may be divided into acute, subacute, and chronic. The acute form is characterized in the first stage by severe abdominal pain, followed by immobility, vomiting, subnormal temperature and shock. In the second stage all the symptoms and signs decrease somewhat in severity, but the abdominal tenderness and rigidity remain. The third stage is that of generalized peritonitis with its concomitant findings. The subacute type is similar to the acute type except that the symptoms are much less severe. The chronic type is usually only recognizable as an ulcer which does not respond to medical treatment.

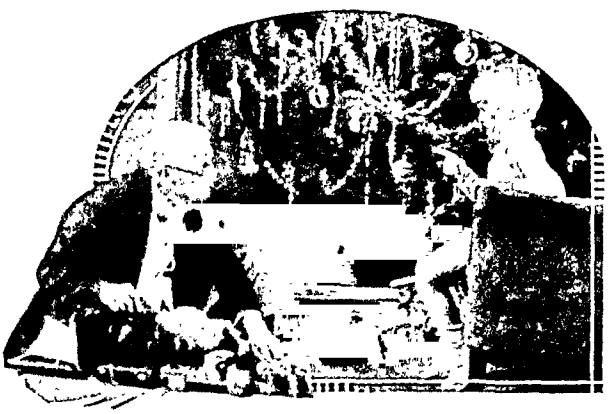
Francis D. Murphy, Milwaukee.

ANDREWS, FRED L. AND WALKER, THOMAS F.

Intestinal Obstruction Due to Ingestion of Dried Peach. J. A. M. A., Vol. 109, pp. 431-432, Aug. 7, 1937.

The authors report the case of a woman who presented herself with the symptoms of severe abdominal pain, nausea and vomiting. She thought she had "ptomaine poisoning." She had

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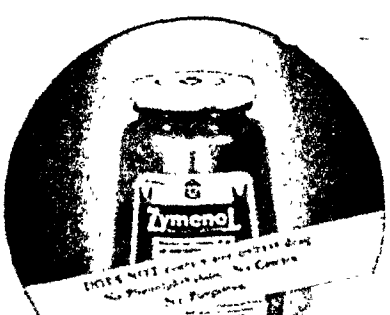


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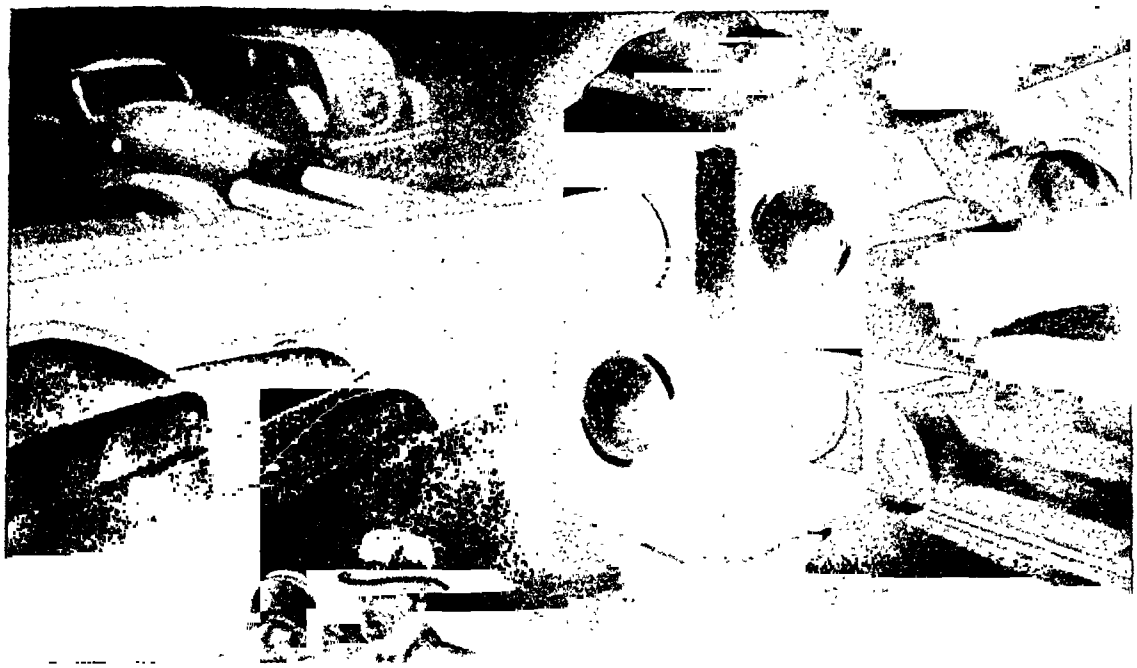
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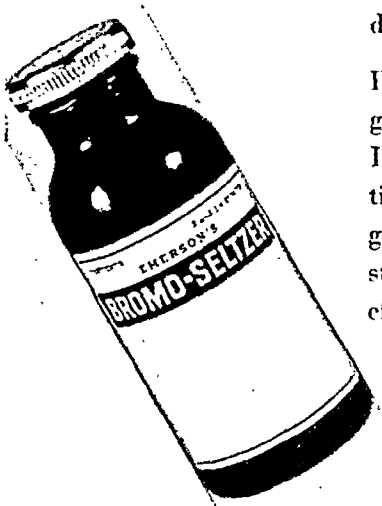
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eaten sardines at noon the day before, also the dried half of a peach which had slipped down her throat. The pain began in the upper abdomen and gradually became more severe. It was not relieved by enemata, either at home or in the hospital. The vomiting gradually became worse, projectile and fecal in character. The temperature was 99° Fahrenheit, the pulse 136, and the leucocyte count, 2,500. At operation, there was found to be a sausage shaped mass obstructing the small intestine. This proved to be a half of a peach which had swollen sufficiently to cause a complete obstruction. The convalescence was uneventful until the fourth day when she coughed and felt something snap. The wound was reopened and part of the incision in the intestine was found open. Bile and fecal material were found in the peritoneal cavity. This opening was resutured and rubber drains were inserted. The patient died the next morning.

Francis D. Murphy, Milwaukee.

THOMPSON, JOHN C.

The Hemopoietic Response Following Oral Administration of Desiccated Duodenal Mucosa. Ann. Int. Med., Vol. 11 (O. S., Vol. XVI), July, 1937.

The author reports that gastrectomy does not promptly produce a primary anemia but in dogs, following an experimental stricture of the small intestine, in man following lateral anastamosis, in chronic intestinal obstruction and in sprue there is produced a blood picture resembling pernicious anemia.

In the summary of seven cases treated with small oral doses of desiccated duodenal mucosa of swine, the author states that as good or better results were obtained than with larger doses of desiccated gastric mucosa as reported by others.

Whereas W. B. Castle obtained his results with desiccated gastric mucosa, the author produced results with desiccated duodenal mucosa of swine. Therefore, Dr. Thompson maintains that the hemopoietic principle is produced in both the stomach and small intestine of swine, and believes that it is reasonable to deduce that the same condition exists in the human.

B. B. Vincent Lyon and
Clifford H. Arnold, Philadelphia.

WAKERLIN, G. E.

The Hemopoietic Liver Principle. Ann. Int. Med., Vol. 11 (O. S., Vol. XVI), July, 1937.

This paper reviews the history of the various blood building liver products, leading up to the hemopoietic principle, and discusses the tests which prove the presence of this principle.

The stomach and the duodenum contribute materially in the formation of the so-called "intrinsic factor" which combines with the so-called "extrinsic factor" of the dietary, to form a third substance which is formed or stored in the liver. Dried stomach and duodenum extractions contain, not the hemopoietic liver principle, but the intrinsic and extrinsic factors.

The intrinsic factor has been found in the gastric mucosa. Only a mild type of anemia follows complete gastrectomy in experimental animals. Deficient vitamin B_1 diet produced macrocytic anemia in monkeys. Gastro-colic fistulae cases in the human; and constriction of the small intestine in dogs generally cause a macrocytic hyperchronic anemia. Destructive liver conditions, reducing the liver cells and thereby the storage capacity of the liver, show a deficiency in the hemopoietic principle, and these cases improve on oral administration of the hemopoietic liver principle.

B. B. Vincent Lyon and
Clifford H. Arnold, Philadelphia.

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Bisiodide is brought to the attention of Gastro - enterologists because it probably is the most easily administered of all effective oral anti-syphilitic drugs. It is tolerated by the most sensitive stomachs.

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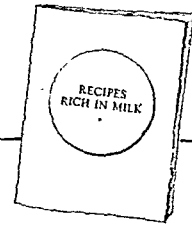


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Other qualities which make Irradiated Pet Milk superior to ordinary milk are: Sterility, precluding the possibility of milk-borne infection; altered whey proteins, less likely to cause allergic disturbance; complemental vitamin D, created by irradiation to facilitate utilization of calcium and phosphorus; lower cost generally than any other form of milk.

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MEANS, J. H., HERTZ, S. AND LERMAN J. *Nutritional Factors in Graves' Disease. Ann. Int. Med., 11:429-436, Sept., 1937.*

The authors as a result of observation and study of some 35 cases conclude that malnutrition is an important factor in precipitating thyrotoxicosis. In 14 of the cases the prethyrotoxic weight loss was occasioned by reduction cures and in the remainder it was due to other factors leading to diet restriction such as, treatment of ulcer, ulcerative colitis, diabetes, and diseases leading to malnutrition.

A distinction is made between general malnutrition due to total negative calory balance and malnutrition due to shortage of specific dietary elements such as vitamins or minerals.

They discuss certain manifestations in Graves' disease which are apparently related to the more specific types of malnutrition. Among these are myasthenia, skeletal decalcification with increased calcium and phosphorus excretion and evidences of iron shortage with smooth tongue, nail changes, and achlorhydria.

They have shown that addition of adequate amounts of vitamin B_1 to the diet in thyrotoxicosis, though not affecting the basal metabolic rate, does cause a marked improvement in appetite and consequent gain in weight. They use it routinely in preparation of such cases for surgery. They also suggest the possible etiological relationship between vitamin B_1 shortage and cardiac insufficiency of thyrotoxic patients. Night-blindness was a prominent symptom in one case of Graves' disease that followed the use of a grossly inadequate diet. It cleared up with the use of an adequate diet.

The authors stress the need for proper attention to the nutritional deficiencies in preparing patients for surgery, and cite a case illustrating this point.

In conclusion they sound a note of warning against too vigorous reduction cures as thyrotoxicosis may be induced thereby. In the matter of diet they suggest the use of vitamin B_1 in preparing thyrotoxic patients for surgery because of its beneficial effects upon the appetite and possible beneficial action upon cardiac function. Excessive protein is considered undesirable because of its specific dynamic action. Carbohydrate in large amounts is insurance against depletion of the glycogen stores of the liver and thus safeguards that organ. Fat may be given as the patient desires.

Malnourished thyrotoxic patients as well as those with psychosis, or cardiac insufficiency are considered poor operative risks. They advise, in addition to the routine pre-operative preparation, therapeutic measures adjusted to the individual's needs.

Hanes M. Fowler, Fort Wayne.

ROBINSON, C. S., CUNNINGHAM, R. S., BLALOCK, A., GRAY, M. E. AND ROGERS, B. C. *Chylous Effusions Produced by Ligation of the Superior Vena Cava: Chemical and Cytologic Studies. Arch. Path., 24:3-501, Sept., 1937.*

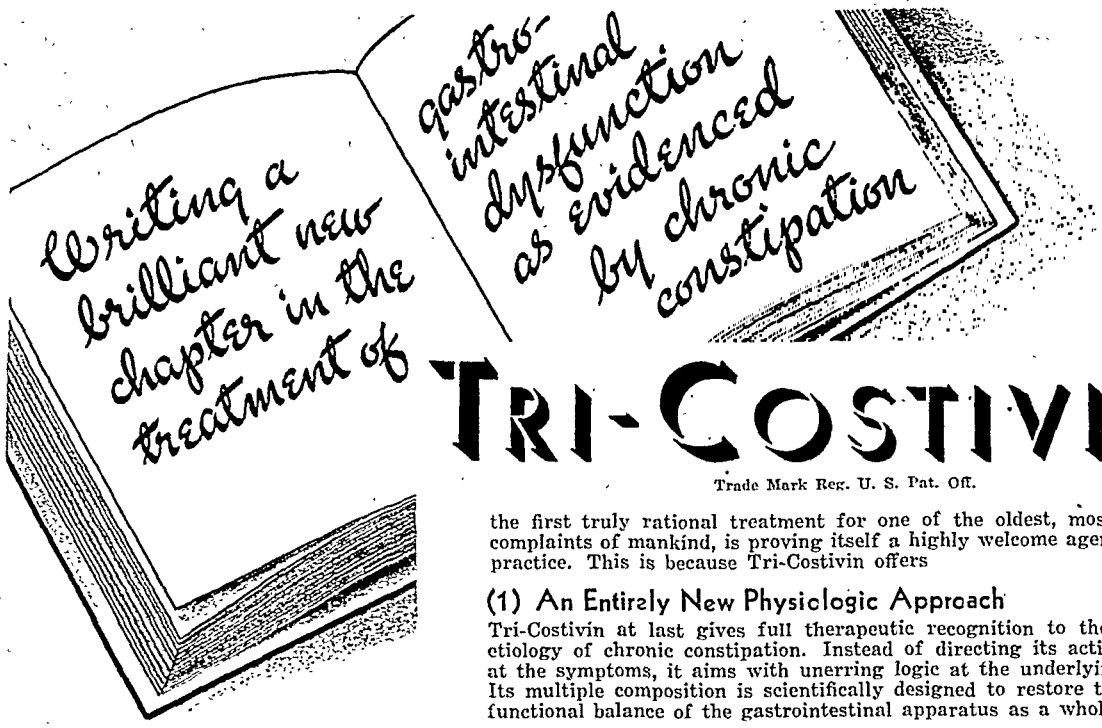
The authors review the meager literature on chylothorax and analyze the references to one hundred cases in man in which the diagnosis seems to be correct. In these cases but meager data on the cellular content of the fluid and on the changes in the cell picture in the blood stream is found.

Chylothorax was produced in twenty-eight of forty-seven animals (dogs and cats) in each of which the superior vena cava was ligated. In eleven animals fluid was obtained from the pleural cavities which was not chylous in character, and in eight animals no fluid developed. Studies were made of the cellular content of the milky fluid and the circulating blood and the chemical constituents of the fluid. They found that the fluids were very rich in lymphocytes and also contained a considerable number of neutrophils. They averaged 20,000 cells, of which about 2,000 cells were neutrophils and about 17,500 cells were lymphocytes.

In the circulating blood of the animals the total number of lymphocytes and the total number of eosinophiles dropped markedly following ligation; the former due probably to the obstruction of lymphatic drainage, but no explanation was found for the drop in the circulating eosinophiles.

The milky fluids obtained were true cholous effusions, the opacity of which was due to free fat. The lipids estimated as "neutral fat" comprised about 80 per cent of the total lipids. The quantities of cholesterol were small but formed a constant fraction of the total lipid. The esterified cholesterol did not vary uniformly with the neutral fat. The total nitrogen values probably included nitrogen from the nonlipid compounds, but the aminonitrogen was due mostly to true lipids and tended to vary with the neutral fat. The phosphatide fraction contained substances which were neither lecithin nor cephalin and these varied with the neutral fat. The phosphorus and the aminonitrogen constants seemed to rise and fall together.

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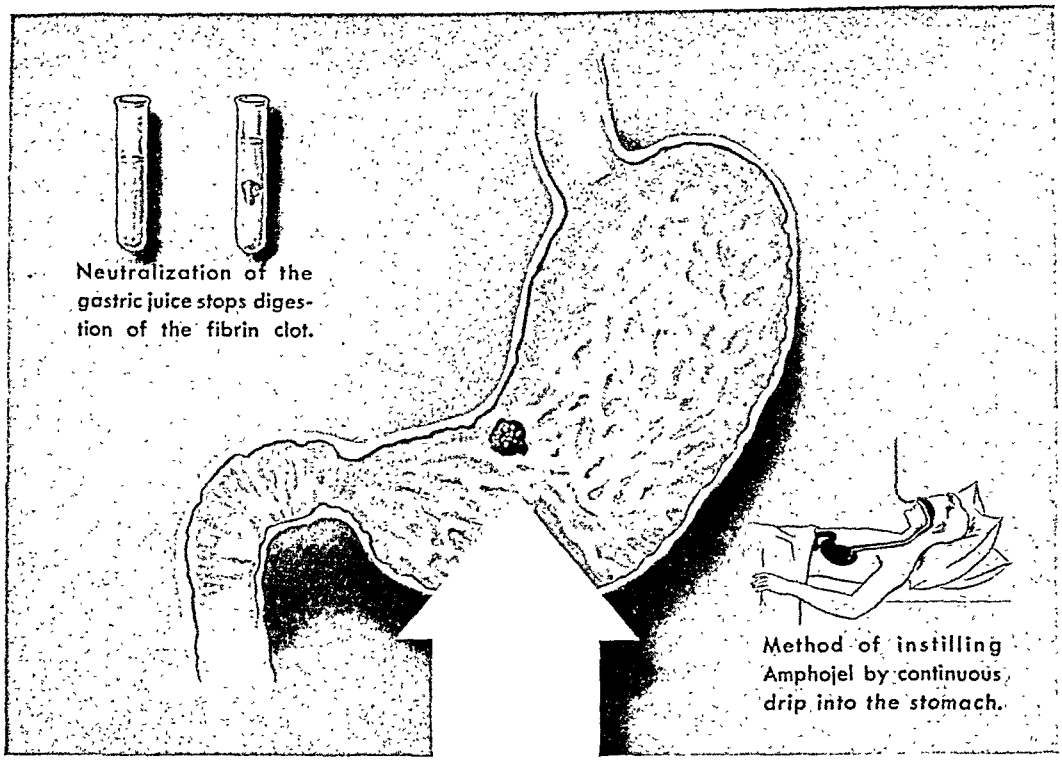
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Ulcer Recurrences Attributed to Upper Respiratory Tract Infection: A Possible Illustration of the Shwartzman Phenomenon*

By

BURRILL B. CROHN, M.D.

and

GREGORY SHWARTZMAN, M.D.

NEW YORK, NEW YORK

VARIOUS factors contribute to frequent recurrences of ulcer activity after periods of remission or apparent cure. Among the most important of these elements, writers generally recognize (1) dietary indiscretion, (2) overactivity, physical or phychic, leading to fatigue or exhaustion, (3) abuse of alcohol, (4) nicotinism, particularly the misuse of cigarettes, (5) seasonal incidence, and (6) probably closely affiliated with the former, upper respiratory, pharyngeal, accessory sinus and other forms of so-called focal infections.

The relative frequency or comparative importance of these several factors has not been statistically computed, insofar as the accepted dictums or the authorized text-books or publications on gastro-enterology are concerned; but that they all play a rôle individually or on occasions is doubted only by the unorthodox. The significance of the abuse of smoking (cigarettes) may perhaps still be in the province of debate, but to the role of infection in predisposing to or actually causing ulcer recurrences, there seem to be no dissenters. Particularly potent in such a causative relationship are infections of the upper respiratory and nasal passages, a fact which is attested by most of the writers of standard works. Rehfuss (1) accepts focal infection in this rôle without hesitation, quoting freely from the experimental work of Rosenow (2), as confirmed by Haden and Bohan (3). Hurst and Stewart (4) warn against sudden exposure and changes of temperature and advise a rapid resumption of active ulcer therapy when a cold threatens to awaken gastric symptoms. Eusterman and Balfour (5) quote not only fully the relationship between focal infections (particularly of the teeth and tonsils) and peptic ulcer, but refer to studies of Rosenow in which experimental ulcer in animals can be reproduced by utilizing bacteria recovered from cases of bleeding ulcer in man.

That duodenal ulcer was particularly susceptible to reactivation in the fall and winter months was attested by Moynihan (6) in his earliest clinical descriptions of that disease, though Hutter (7) has been able to find no variations of climatology, humidity, altitude or temperature fluctuations to account for the phenomenon. Christiansen (8) notes an even distribution of ulcer recurrences with hemorrhage throughout the months of the year, though most Scandinavian authors find between 35 per cent and 46 per cent of hemorrhage occurring during the fall months of September and December. Emery and Monroe (9) in evaluating the relative importance of the various factors which cause ulcer recurrences enumerate them as follows:

Of 1279 cases, ulcer activity was reawakened in 334 by fatigue; in 258 by emotion, in 167 by infection (colds and grippe rather than frank pneumonia) and in 37 by dietary indiscretions.

Personally, we feel that these figures of Emery and Monroe understate the frequency with which infective agencies cause a lighting up of a healed ulceration, particularly in years such as the present one (1937) in which bulletins of the Public Health Services publish an annual incidence and a greater severity of grippe, tonsilitis, and upper respiratory infections.

While unable to quote actual figures we have always been convinced of the malign influence of tonsillar infections, acute naso-pharyngitis, grippe, influenza, pleurisy and even pneumonia, bronchial and lobar, in activating ulcer recurrences. It has always seemed a hopeless cause to preserve an apparently healed ulcer case in the presence of a susceptibility to recurrent head colds or chronic sinusitis. Not infrequently a tonsillectomy or a tooth extraction may be followed by an ulcer recurrence. "In a case of gastric ulcer which had been under observation for about two years, and which had shown a disappearance of a penetrating niche with subsidence of all clinical symptoms, there developed a lobar pneumonia. During the convalescence hematemesis and melaena occurred with a renewal of the symptoms" (10) and with a reappearance of the niche.

During the present year of 1937, particularly during the months of February and March, the grippe was unusually prevalent and unusually severe. During that time, and shortly thereafter, a number of cases of hematemesis and melaena of a severe grade were admitted to the hospital for urgent treatment of that complication of ulcer. At one time, within a period of ten days, seven actively bleeding ulcers were seen at the height of the grippe epidemic. In another large city institution as many as eleven ulcer hemorrhages were admitted during the same period.*

The causal relationship between grippe and ulcer hemorrhage became an alarming fact, to such an extent that all latent ulcer cases were warned to avoid coughs and colds lest ulcer recurrence with hemorrhage occur. That this advice was timely was succinctly shown in the case of a young man who, in his third week of Sippy treatment, when free of all digestive complaints, developed a severe head cold. He was

*From the Medical Services and the Laboratories of The Mount Sinai Hospital, New York City, N. Y.

Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, June 7 and 8, 1937.

*Personal communication of Dr. Mostkowitz, of the Staff of the Queens General Hospital, Jamaica, L. I.

immediately warned to take to his bed, disregard the cold, avoid aspirin or other irritating medications or drinks, and to return to the first week of strict Sippy diet with the resumption of his alkaline medication. In spite of this warning and its strict obedience, a gross gastric hemorrhage resulted within 21 hours, necessitating urgent hospitalization.

The relationship between bacterial infection and ulcer hemorrhage was further suggested by an interesting set of facts. The patient, a physician and an accurate observer, reported that in 1926 he had had a series of prophylactic injections of typhoid vaccine. In May, 1936, ten years later, he was given the first of another series of typhoid inoculations. By a mistake in dosage he was given, in the first injection, a triple overdose. Within 24 hours he vomited a gross amount of blood, noted hematuria and petechial hemorrhages over his lower extremities. Coincidentally he developed postprandial distress and night pains. An X-ray carefully read showed an irregular defect of the duodenal bulb. On the occasion of a subsequent hemorrhage in February, 1937, and because of continuous digestive pain and distress, operation was considered indicated. A partial gastrectomy revealed a penetrating duodenal ulcer.

The explanation of the possible causal relationship between bacterial infection and ulcer recurrences with hemorrhage leads to several interesting hypotheses. In the cases of upper respiratory infections with active bacterial invasions, a direct esophageal approach to the stomach through infectious saliva and swallowed secretory discharges must be considered; or an indirect hematogenous route may well be imagined and given credence. This explanation would only apply if we were to regard the ulcer in the peptic mucosa as an active infective focus or site of potential infection, a view which is not generally held.

The case of the physician in which the injection of a dead bacterial vaccine was the apparent factor in activating a peptic ulcer seems to offer a clue to a more satisfactory hypothesis; namely, the phenomenon of local skin reactivity to bacterial filtrates.

Before attempting this correlation the following basic experiments concerning the phenomenon should be recalled:

The phenomenon is elicited by combination of two injections of bacterial filtrates, i.e., preparatory injection into a tissue and provocative injection into the blood stream. The interval of time necessary ranges between 8 to 120 hours, optimum being 24 hours. No specific relationships exist between the preparatory and provocative injections. Bacterial products producing the phenomenon for themselves produce it for each other. The bacterial factors producing the phenomenon, however, are specifically neutralized by immune sera. It is interesting, therefore, that the phenomenon is both non-specific and specific, antigenically specific substances of a great variety producing the same type of injury in the animal tissue by means of the same mechanism (11).

While most of the work on the phenomenon was done thus far with bacterial filtrates, substantial evidence exists that infections are also capable of eliciting the state of reactivity of the phenomenon. The phenomenon was produced at sites infected with streptococcus hemolyticus (Shwartzman (11)), B. anthrax (Gratia and Linz (12)), vaccinia virus (Gratia and Linz (13) and Koplik (14)), B.C.G., pseudotuberculosis of guinea pigs (P. Bordet (15)) and Debonera, Tzortzakis and Falchetti (16)), virulent tubercle bacilli (P. Bordet (17), Freund (18) and Shwartzman (11)), pneumococcus (Michelazzi (19)), B. influenza and B. Bordet-Gengou (Witebsky and Salm (20)), etc.

Thus, at certain stages of infection with the foregoing bacteria and viruses, tissues assume a state of reactivity of the phenomenon under discussion. While this state of reactivity exists, bacterial factors introduced into the general circulation produce lesions characteristic of the phenomenon in the reactive sites. As already mentioned, no specific relationships exist between the provocative factors and those responsible for the local state of reactivity. The lesions obtained bear certain characteristic features in the gross and histologically. They are predominantly hemorrhagic and apparently due to marked capillary fragility similar to hemorrhagic diathesis. The profuse capillary bleeding is associated with severe necrosis, thrombosis and considerable inflammation. It is justifiable, therefore ,to assume that a similar mechanism of production of injury may exist in animal and human pathology of spontaneous diseases associated with hemorrhagic manifestations.

The opinion has been already voiced that purpuric manifestations of acute infectious diseases produced by bacteria and viruses may be due to the mechanism illustrated by the phenomenon of local tissue reactivity (small pox, measles, typhoid fever, meningococcus meningitis, etc.). Previous observations of various authors bring supporting evidence to the assumptions of this sort. Thus, Ikeda (21) in reporting a series of 131 cases of purpuric small pox noted that nearly all the cases had streptococcus bacteremia and that streptococcus could be cultured with regularity from hemorrhagic pox but that the non-hemorrhagic ones were always sterile. According to Koplik (14), in experimental vaccinia infections, a spontaneous transformation of a mild lesion into a hemorrhagic one may be due to a superimposed bacterial infection.

In direct relation to this topic also stand the observations of Ichikawa (22), who reported that intravenous administration of typhoid vaccine into typhoid fever patients brings about a critical drop in temperature not infrequently associated with bleedings in the intestines, lungs, nose and hemorrhage in the skin.

The clinical observations already discussed suggest that a mechanism as described in the foregoing may also, at least in part, be responsible for exacerbations, perforations and bleedings in gastric ulcers. Whatever the primary etiologic factor of gastric ulcer may be, secondary bacterial invaders are commonly found in the bed of gastric ulcers. These bacterial invaders may be, then, responsible for a lasting state of reactivity in the tissues of the gastric ulcer. Once this state of reactivity exists viruses and bacteria-producing infections in organs distant from the gastric ulcer may be able to produce injury in the ulcer by way of the general circulation. The lesion obtained by means of this mechanism should, as already mentioned, consist of necrosis and hemorrhage, i.e., precisely of the type found in bleeding and perforated gastric ulcers. Assumption of this sort is further supported by the fact that the phenomenon of local

tissue reactivity was successfully produced also in the gastric mucosa by Karsner, Ecker and Jackson (23).

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DISCUSSION

DR. ALBERT F. R. ANDRESEN (Brooklyn, N. Y.): This paper and the previous discussions have brought to mind the many times that Fenton Turck appeared before this Society and demonstrated the production of gastric ulcer as a result of the sloughing out of areas of focal necrosis in the stomach mucosa following the injection into animals of his cytost or cell toxin, an extract of dead tissue of the animal or another animal of the same species. I have long felt that the obvious connection between focal infection and peptic ulcer could best be explained on the basis of the absorption of cytost from the focus, rather than by direct infection, as suggested by Rosenow. I feel that the phenomena demonstrated in the present paper could be explained just as well on the basis of the development of a new ulcer at or near the site of the previous ulcer as on the theory of reactivation or sensitization of a previous ulcer. Lewis Gregory Cole has demonstrated conclusively that each attack of ulcer symptoms represents the development of a new ulcer. We are coming constantly nearer to the solution of the ulcer problem.

DR. ASHER WINKELSTEIN (New York, N. Y.): The ideas of Dr. Crohn and Dr. Shwartzman are of great importance, particularly in relation to the question of the erosive gastritis which interests us so much in the ulcer problem.

I should like to cite very briefly three cases that I saw recently. One was a man who had been treated after five years of ulcer symptoms, quite thoroughly, and lost his symptoms for several months. Then he had eight teeth extracted. Twenty-four hours later he had a severe gastric hemorrhage and a marked recurrence of ulcer symptoms. Partial gastrectomy was performed. In addition to old scars, three fresh ulcers and a severe gastroduodenitis were found in the specimen.

The second case was that of a man with a chronic ulcer who had been without symptoms for two years. He then had a severe grippe. On the fourth day, a hemorrhage occurred from the stomach and rigidity appeared in the upper abdomen.

The third case was a man with penetrating duodenal ulcer, with some pyloric obstruction. He was transferred to the surgical service, and, as he was about to be operated upon, he developed a facial erysipelas. With sunlight therapy he recovered and also lost his ulcer symptoms. His operation was cancelled. It is now several months since his discharge and he is perfectly well.

The problem that arises first is whether this activation of ulcer symptoms isn't really the direct effect of toxins or organisms on the mucosa rather than a Shwartzman phenomenon. Knud Faber has shown that during influenza you frequently get a severe gastritis and duodenitis.

The second question comes up as to whether it really is the phenomenon. I think it is in most instances. The phenomenon explains the activation of the symptoms probably by lighting up the associated gastritis rather than the ulcer itself.

Another point comes up as to whether an intercurrent infection may not improve the ulcerative gastritis and the ulcer by provoking an increased immunity. This may have been the case in the patient with the erysipalas. Also, the phenomenon may in itself promote healing (Shwartzman). man).

DR. BURRILL B. CROHN (New York, N. Y.) (closing the discussion): Dr. Shwartzman pointed out that in the mechanism of the phenomenon, necrosis takes place before inflammation; this may explain one point, namely, the incidence of hemorrhage as an initiatory symptom in recurrence of ulcer.

Studies in Mucous Membrane Hypersensitiveness

III. The Allergic Reaction of the Passively Sensitized Rectal Mucous Membrane*

By

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and

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IN previous investigations (1, 2) the allergic reactions of the passively locally sensitized ophthalmic and nasal mucous membranes were studied. The present communication deals with the allergic reaction as it occurs in the rectal mucous membrane which has been passively sensitized. This site was chosen for study because it represents the only accessible portion of the gastro-intestinal mucous membrane. It is, however, quite characteristic in structure and fairly representative of the lining of the entire intestinal tract.

* Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, June 7 and 8, 1937.
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TECHNIC

The technic employed in this study is similar to that used in the investigations on the eye and nose. It is a modification of the immunologic procedure employed by the authors in their studies on the absorption of unaltered protein (3). It consists of sensitizing the rectal mucous membrane to peanut protein by the local injection of a human serum containing reagin antibodies for peanut. Twenty-four to forty-eight hours later, the peanut antigen is ingested on a fasting stomach. Within a few minutes an inflammatory reaction usually develops at the sensitized sites in the rectum. As pointed out in previous communications (4), this signifies the presence of the unaltered peanut protein in the circulation and represents the allergic reaction of the sensitized mucous membrane to specific excitation by the circulating peanut antigen.

A—Passive Local Sensitization of the Rectal Mucous Membrane.

1. Sensitizing Serum: Peanut was selected as the antigen to be investigated solely because a serum which was particularly suitable for the study of this antigen happened to be available. It was obtained from a patient who manifested a very marked positive reaction to a skin test with peanut antigen and who developed immediate severe constitutional symptoms following the ingestion of this food. His serum showed a very high titer for reagin antibodies to peanut and was used in a dilution of 1 to 10 for sensitizing purposes.

2. Site of Sensitization: The rectal mucous membrane was sensitized at a distance of 2, 4 or 6 cm. from the anus. In some of the cases, the mucous membrane of an internal hemorrhoid was the site of sensitization. In every subject the skin on the forearm was also injected with the serum for purposes of control and comparison.

3. Technic of Sensitization: All forms of nuts were excluded from the subject's diet for a period of twenty-four hours previous to the sensitizing injection. The rectal mucous membrane was visualized with the aid of a rectal speculum. About 0.05 c.c. of the sensitizing serum was introduced into the mucous membrane on either the posterior or anterior wall of the gut. A 27 gauge needle was employed for the purpose and the procedure was seldom followed by any bleeding or subjective symptoms.

B—Administration of the Protein Meal.

One or two days after sensitization the patient reported without breakfast and was given the peanut meal. This was administered orally in most instances and consisted of 10 grams of raw ground peanuts in 30 c.c. of water to which was added 1 gram of sugar and 0.05 c.c. of oil of cloves. In a small series of cases, the meal was introduced into the rectum or was directly applied on an applicator to the sensitized rectal site.

THE REACTION FOLLOWING ORAL ADMINISTRATION OF THE ANTIGEN

Following the administration of the peanut meal reactions developed at the sensitized cutaneous and mucous membrane sites. In most instances the reaction of the mucous membrane preceded that of the skin by several minutes. The reaction on the skin, as has been described in previous communications (5), consisted primarily of erythema and wheal formation and was usually preceded and accompanied by marked pruritis. The reaction at the sensitized sites in the rectum consisted of edema and hyperemia. The subjective symptoms associated with its development varied with its location. Generally speaking, the nearer the sensitized site was to the anus, the more pronounced were the subjective symptoms caused by the allergic reactions.

The onset of the local allergic reactions was usually heralded by the appearance of symptoms such as pruritis, burning, a sense of fullness, and a desire to empty the bowel. On proctoscopic examination, the development of an edema involving the sensitized site was the first objective finding. The edematous mucous membrane was at first paler than the contiguous mucosa. Within five minutes after its onset, the edema had reached its peak. Several minutes after the appearance of the edema, a hyperemia started to develop. This gradually grew in intensity for about ten minutes, the mucous membrane at the sensitized area becoming deeply congested. The inflammatory process was confined to the neighborhood of the sensitized site which acquired a much deeper color than that of the normal mucous membrane. Associated with these changes there was an increase in mucous secretion over the affected area. The reaction reached its peak about fifteen or twenty minutes after its onset and then gradually began to subside. All traces of it were usually lost in about an hour. Several examinations of the mucous secretion produced by the allergic reactions failed to show the presence of any eosinophiles. Attempts to aspirate fluid from the edematous area were unsuccessful.

On six subjects an internal hemorrhoid was the site of sensitization (Table I, Cases 1-6, inclusive). In two-thirds of these cases, the mucous membrane reaction preceded that on the skin by two or three minutes. Pruritis accompanied the reaction in five cases. A sense of fullness in the rectum and a desire to empty the bowel were present in two patients. Only one complained of a burning sensation in the rectum. Objectively, the reactions all showed characteristic edema and hyperemia.

In ten subjects, the mucous membrane of the rectum was sensitized 2 cm. from the anus (Table I, Cases 7-16, inclusive). In all but one, the allergic reaction in the rectum preceded that of the skin by several minutes. The subjective symptoms differed from those of the previous group in that pruritis was less commonly noted. A sense of rectal fullness was reported by seven of the group. Desire to empty the bowel was experienced by six patients and three complained of burning in the rectum. Objectively edema and hyperemia were present in all ten subjects.

In eight cases, the rectal mucous membrane was sensitized at a site 4 cm. from the anus (Table I, Cases 17-24, inclusive). Five of these patients complained of varying degrees of fullness in the rectum and two complained of burning. Pruritis was present in only one patient. The subjective symptoms in this group were less pronounced than those reported by the preceding groups, in whom the allergic reactions were closer to the anus.

In fourteen subjects, the rectal mucous membrane was sensitized 6 cm. from the anus (Table I, Cases 25-38, inclusive). The subjective symptoms in this group were relatively few. Pruritis was present in two cases and two others complained of fullness in the rectum. Rectal burning and a desire to empty the bowel was not reported by any of this group. The objective findings at the 6 cm. level were more difficult to observe through the proctoscope than in the preceding groups. In all respects, however, they are the same as those already described.

In the twenty-two cases in which the local reaction occurred at the 4 and 6 cm. levels, the average reaction time of the mucous membrane was about the

same as that of the skin. In the preceding groups, where the sensitized sites were nearer the anus, the mucous membrane reaction usually preceded that at the cutaneous site by several minutes. It is not improbable that the difficulty in detecting the exact time of the onset of those reactions which occurred higher up in the rectum is responsible for the apparent delay in reactions at these levels.

RECTAL ADMINISTRATION OF THE PEANUT ANTIGEN

In eight subjects, the antigen was introduced into the rectum (See Table II). In three instances, the full protein meal was given. In five subjects a cotton swab saturated with several cubic centimeters of the peanut meal was locally applied to the sensitized mucous membrane site. In three of these cases, this

TABLE I

Summary of results following oral administration of antigen

Case No.	Diagnosis	Site of Sensitization	Absorption Time in Minutes		Subjective Symptoms			
			Skin	Rectal	Pruritis	Fullness	Desire to empty bowel	Burning
1	Gastric Neurosis	Int. Hem.	17	15	x			
2	Hemorrhoids Combined	Int. Hem.	11	12	x			
3	Chronic Cholecystitis	Int. Hem.	5	6	x			
4	Gastric Neurosis	Int. Hem.	17	15	x	x	x	
5	Ulcerative Procto-Sigmoiditis	Int. Hem.	15	12		x	x	x
6	Carcinoma of Pancreas	Int. Hem	16	14	x		x	
7	Cholelithiasis	2 cm.	9	6		x	x	
8	Duodenitis	2 cm.	19	11				x
9	Chronic Cholecystitis	2 cm.	11	10		x	x	
10	Duodenal Ulcer	2 cm.	25	25				x
11	Ca. Greater Curvature of Stomach, non-obstructive	2 cm.	11	10			x	x
12	Hypertensive Arteriosclerotic Heart Disease	2 cm.	18	15		x	x	
13	Chronic Cholecystitis	2 cm.	10	8		x	x	
14	Chronic Cholecystitis	2 cm.	16	18		x		
15	Chronic Cholelithiasis and Chronic Appendicitis	2 cm.	29	25		x		
16	Chronic Cholecystitis	2 cm.	20	18	x	x	x	
17	Gastric Ulcer	4 cm	20	16		x		
18	Pernicious Anemia	4 cm	13	12		x		
19	Carcinoma Colon	4 cm.	19	20		x		
20	Duodenitis	4 cm.	21	21		x		
21	Chronic Cholecystitis	4 cm.	15	18		x		
22	Chronic Cholecystitis	4 cm.	18	20	x			
23	Internal Hemorrhoids	4 cm.	19	20				x
24	Chronic Cholecystitis	4 cm.	20	22				x
25	Hypochromic Anemia	6 cm.	25	—				
26	Gastric Neurosis	6 cm.	7	9		x		
27	Gastric Neurosis	6 cm.	17	15				
28	Chr. Lead Poisoning	6 cm.	17	16				
29	Visceroptosis	6 cm.	17	20				
30	Duodenal Ulcer	6 cm.	16	15				
31	Duodenal Ulcer	6 cm.	25	25				
32	Proctitis	6 cm.	10	12				
33	Visceroptosis	6 cm.	19	20				
34	Chronic Cholecystitis	6 cm.	17	20				
35	Ca. of Stomach	6 cm.	15	14	x			
36	Duodenal Ulcer	6 cm.	25	30				
37	Duodenal Ulcer	6 cm.	16	17	x			
38	Duodenal Ulcer	6 cm.	22	15		x		

swab was left in situ; in the remaining two it was withdrawn.

In the three cases in which the entire meal was administered by rectum the reaction seemed to develop in the same manner as noted after oral administration of the antigen. However, in subjects 14 and 15, who had been tested on separate occasions by both methods of antigen administration, the reaction time was shorter by several minutes with the rectal than with the oral technic (See Table II).

TABLE II

Summary of results following rectal administration of antigen

Amount of Antigen	Case No.	Diagnosis	Site of Sensitization Distance from Anus in cm.	Reaction Time in Minutes		Subjective Symptoms			
				Skin	Rectal	Pruritis	Fullness	Desire to empty bowel	Burning
Full meal	39	Bleeding Duodenal Ulcer	6	23	20				
Full meal	*14	Chronic Cholecystitis	2 (2)	17 (16)	15 (18)		x (x)		x
Full meal	*15	Chronic Cholelithiasis	2 (2)	33 (29)	24 (25)		(x)		
Cotton swab	40	Visceroptosis	2	20	15		x		
Cotton swab	41	Internal Hemorrhoid		19	16		x	x	
Cotton swab	42	Internal Hemorrhoid		16	10		x		x
Cotton swab	43	Lead Poisoning	4	22	18				
Cotton swab	44	Colitis	4	14	10				

*Readings in parenthesis represent results following oral administration of antigen in same patient.

In the five subjects in whom a minimal amount of the peanut meal was applied on a cotton swab solely to the sensitized site, the allergic reactions which developed were similar in character to those noted when the full meal was administered either by rectum or given by mouth. These reactions, however, did not reach their maximum until after the skin reaction had appeared.

DISCUSSION

In previous investigations (1, 2) it has been shown that the external mucous membranes in normal humans, such as those of the eyes and nose may be passively and locally sensitized by the injection of human reagin-bearing sera. In the present communication the writers have demonstrated that the rectal mucous membrane may be similarly sensitized. The fact that reagins can be fixed in the mucous membrane of the gastro-intestinal tract as well as in those of the ophthalmic and respiratory organs, suggests the universality of reagin fixation in human mucous membranes.

In the ophthalmic and nasal studies, the allergic reactions were usually elicited by the external or direct application of the related offending antigens to the sensitized mucous membranes. In the present study, however, they were produced by the oral administration of the antigen as well as by its local application. The ingested antigen reached the sensitized site by way of the circulation. This, no doubt, is the manner in which antigenic stimulation of allergic mucous membranes occurs in many forms of food hypersensitiveness.

The cardinal and constant characteristics of the allergic reactions in the passively sensitized mucous membrane of the rectum are essentially the same as those which were observed in the allergic reactions of other mucous membranes. They consist of edema, erythema and increased mucous secretion. The allergic reaction of the passively sensitized rectal mucous membrane is short-lived and disappears within an hour. A strong reaction usually neutralized the fixed antibodies so that, on subsequent feeding of the antigen, no further local reactions occur. Occasionally, however, a second mild reaction may be obtained upon restimulation of the site.

The allergic reaction of the rectal mucous membrane was associated with symptoms which varied with the individual and with the site of sensitization. They included such complaints as pruritis, rectal fullness, desire to empty the bowel, and burning. The closer the inflammatory reaction of the mucous membrane was to the anus the more severe were the complaints. Usually the subjective symptoms preceded the appearance of the local reaction. Pruritis was present in most of the patients in whom the reaction occurred on a sensitized internal hemorrhoid. Fullness and desire to empty the bowel was a more common complaint when the reaction occurred at a distance of 2 or 4 cm. from the anus. When reaction was at the 6 cm. level, the paucity of subjective symptoms was quite noticeable.

The local application of the antigen to the sensitized sites in the rectum revealed some findings which illustrate the possible mechanisms which may be involved in gastro-intestinal allergy in humans. It was noted that, on the rectal administration of the antigen, the edema at the sensitized site began to develop slowly. This reaction preceded the lighting up of the control site on the skin by as much as six minutes. With the appearance and development of the cutaneous reaction, the edema and erythema at the rectal site became more intense and rapidly reached its height. This sequence of events was the same when the entire meal was introduced in the rectum and when only a small amount

of it was applied on an applicator to the sensitized site. It suggested the probability that the amount of antigen in contact with the mucous membrane was not necessarily more important in determining the intensity of the reaction, than the amount that reached the sensitized site by way of the circulation. The fact that the local reaction did not reach its maximum until there were evidences of a general systemic dissemination of the antigen emphasizes the importance of this factor in the mechanism of food allergy symptoms in humans. It is quite evident, therefore, that in considering the mechanisms by which food or drugs may cause allergic manifestations, there are three possibilities to be considered: first, that symptoms may result from the direct intimate contact of the offending allergen with the sensitized mucous membrane; secondly, that the reaction of the sensitive mucous membrane may be the result of stimulation from an antigen which had been absorbed into the circulation from another part of the gastro-intestinal tract; and thirdly, that both mechanisms may be jointly involved. The fact that an antigen may cause disturbances of sensitive mucous membranes, locally and at a distance, within the period of a few minutes, may explain some of the bizarre and unusual clinical pictures which sometimes occur in food allergy.

CONCLUSIONS

1. The rectal mucous membrane can be passively and locally sensitized with human reagin-bearing sera.
2. The allergic reaction can be induced by either the oral or the rectal administration of the antigen.
3. The allergic reaction consists of edema, hyperemia, and increased mucous secretion.
4. Subjective symptoms, such as pruritis, burning, a sense of fullness, and a desire to empty the bowel, are commonly associated with the allergic reaction and vary with its location.
5. The allergic reaction in the sensitized mucous membrane of the gastro-intestinal tract may be induced by antigen which is in direct contact with it or by absorbed antigen which reaches it via the circulation or by both.

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DISCUSSION

DR. ALBERT F. R. ANDRESEN (Brooklyn, N. Y.): This beautiful and very important presentation has demonstrated to us the nature of the reactions that take place in the gastro-intestinal tract in allergy. I think it is one of the most beautiful demonstrations that I have ever seen. It shows us that the reactions in the gastro-intestinal tract may be due not only to local contact with the food to which a patient has been sensitized, but that they are probably more frequently due to absorbed food antigen in the circulating blood. The rapidity with which absorption has taken place is one of the remarkable things demonstrated. Within twelve or fifteen minutes after ingestion, the reaction was noted at the rectum.

Some clinicians have doubted that pruritus ani could be due to food allergy, because the irritation occurred so soon after the food was taken, but we have been shown that direct absorption of the food protein, unchanged, takes place with great rapidity.

The rectal symptoms usually attributed to allergy, pruritus ani, and even actual ulceration, can easily be understood when we conceive of repeated insults to a rectal mucous membrane permanently sensitized, and we can easily understand how even severe conditions like ulcerative colitis are so frequently caused by a food allergy. On the other hand, bacterial allergy might be the explanation for similar phenomena occurring in the stomach as were shown by Dr. Crohn and Dr. Shwartzman in a previous paper today.

This paper is another very important contribution to the subject of food allergy and helps us to understand better what is going on in a sensitized individual.

I compliment the authors on what they have done.

DR. T. T. MACKIE (New York, N. Y.): I should like to echo Dr. Andresen in congratulating Dr. Gray and Dr. Walzer on the work which they have presented here this morning. We have had a good many reports in recent years in the clinical literature indicating the validity of so-called food allergy in the intestinal tract. This paper which has been presented this morning is one of a group of studies which Dr. Walzer and his associates have carried out, which present the first objective experimental evidence demonstrating the validity of the allergic mechanism in the intestine.

To be sure, it is passive sensitization, which is not the mechanism which would be involved in the production of symptoms in the human being. As yet no one has succeeded in producing active sensitization. It would appear, however, that this is merely a matter of time and of devising a satisfactory technic. This study and the others which fall in the same group, constitute definite proof that the intestinal tract, including the stomach and areas below, to the rectum, may properly be spoken of as a shock organ.

The implications of this work, I think, are very great, and again I should like to congratulate the authors.

DR. ARTHUR J. ATKINSON (Chicago, Ill.): I should like to substantiate Dr. Gray's observations. We have produced a similar phenomenon and acute ulcers in dogs in an exteriorized segment of the colon, by actively sensitizing dogs to various foreign proteins, by injecting these foreign proteins intravenously and subsequently injecting the same protein in an exteriorized segment of the colon.

In some of the dogs ulcers developed, but we could not make these ulcers chronic. They would heal in spite of subsequent injections. All the dogs did not show ulcerations although they did show the same type of phenomena that Dr. Gray had pointed out.

This work was done after Dr. Ivy had produced ulcers of this type in the stomachs of dogs by active sensitization.

DR. A. C. IVY (Chicago, Ill.): Mr. Chairman, there is one question which I have in mind which I should like to put to Dr. Gray and see whether he can answer it. It is: I obtained the impression that the sensitization he observed did not last very long, and desensitization resulted. That is exactly what we observed in the allergic ulcers we produced a number of years ago in the pyloric mucosa, and in the duodenal mucosa. Continued administration of the antigen produced desensitization. Now, if allergy plays an important role in the human being in the production of pruritus ani and of ulcers in the colon and stomach, I wonder why some sort of desensitization process does not occur and lead to the spontaneous relief of the condition.

DR. B. M. BERNSTEIN (Brooklyn, N. Y.): From the

point of view of desensitization, there are two cases I should like to report. One is that of a doctor, who had an ulcer for a number of years and suddenly found he had hay fever. During the time he was getting pollen injections, he had no pains of any kind. He then found that every time he had an upper respiratory infection, if he didn't take any pollen, he had pains; if he took pollen, he had no pains.

Another man only recently came into the office with recurrence of severe ulcer symptoms. For a number of years he had had recurrences only during the time he had upper respiratory infections. I was giving him nonspecific therapy. During the course of injections he had a severe upper respiratory infection and yet in spite of that, had no recurrence of symptoms.

I think these two cases show the desensitization phenomenon. We combine the Shwartzman phenomenon and the allergic factor at the same time.

DR. IRVING GRAY (Brooklyn, N. Y.) (closing the discussion): I wish to thank Drs. Andresen, Mackie, Atkinson, Ivy and Bernstein for their discussion of our presentation.

In our studies we have shown that the mucous membrane of the gastro-intestinal tract can be passively and locally sensitized. We have had the opportunity of presenting to you the phenomena associated with the local allergic reaction in the mucous membrane of the rectum, colon and ileum. While the clinical symptoms of gastro-intestinal allergy have been recognized we believe that this is the first time as stated by Dr. Andresen that edema and hyperemia of the human gastro-intestinal mucous membrane has been experimentally produced and demonstrated.

Dr. Mackie has been interested in the subject of active sensitization. This field of investigation in immunology has attracted the attention of many investigators but to date little has been accomplished. The work that Dr. Atkinson has cited in experimental studies on the colon of dogs is interesting but we have had no experience in this type of investigation.

Dr. Ivy has raised the question of desensitization. This subject has been widely studied by the allergists and I believe that it is the accepted opinion today that treatment directed toward specific hypersensitiveness as it occurs in hay fever or food hypersensitiveness may bring about improvement or cessation of objective symptoms by some alteration in the shock tissue. The fact remains that on the study of the blood serum after such successful treatment, the reagin antibody content remains essentially the same.

In our present communication we have called attention to the fact that after passive sensitization of the mucous membrane, administration of the antigen is followed by an allergic reaction which usually neutralized all the antibody at the site of the injection. It is pertinent at this time to point out that the reagin antibody is fixed in the tissues at the site of local injection and is not absorbed.

The allergic reaction which we have described in this presentation, as previously demonstrated by Dr. M. Walzer, is due to the absorption of the whole unaltered protein into the circulation and its reaction at the local site of sensitization. The recent experimental work on dogs by Alexander, Shirley and Allen conclusively proves that unaltered protein is absorbed into the general circulation by way of the lymphatics emptying into the thoracic duct. Those studies are important because they show that whole protein reaches the general circulation in not insignificant amounts without passing through the liver. The allergic reaction as described in our communication is brought about by the reaction in the passively sensitized tissues between the injected antibody and the related protein which has been ingested and absorbed in an unaltered state. Alterations in X-ray patterns of the stomach and colon following the administration of barium to which had been added the specific excitant in allergic individuals has been recently reported by Fries and Zismore of the Walzer clinic in their studies in allergic children.

We are hopeful that from all these various studies further progress in the field of gastro-intestinal allergy will be made.

Secondary Effects of Radiation Upon the Rectum Following the Treatment of Extrarectal Pelvic Lesions*

By

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GREAT advances have been made in the treatment of malignancy of the uterus, prostate and bladder by the use of radium and cross fire roentgen-ray therapy. The action of these therapeutic agents, however, cannot always be confined to the organ involved in the malignant process. It is not surprising, therefore, that the irradiation should affect the rectum. The proximity and fixation of this structure in the pelvis has resulted not infrequently in secondary effects, which may be mistaken for an extension or recurrence of the malignancy, and in symptoms which may make the cure seem worse than the disease.

Buie and Malmgren (1), in 1930, reported a study of 65 patients after irradiation therapy in the pelvis. They described the lesions and the symptoms and outlined treatment by rectal irrigations and instillations. Jones (2) in 1932, again mentioned the rectal and bladder complications encountered in the treatment of carcinoma of the cervix. He spoke of two types of rectal complications, the early, characterized by frequency of defecation and tenesmus, and the late, which was often mistaken for a recurrence of the malignancy. In the later type, severe pain, tenesmus, and blood and mucus in the stools were prominent symptoms. He pointed out that digital examination was extremely painful, and that on proctoscopic inspection, ulcers, scars and telangiectases were noted in the rectum at the level of the cervix. Later, Jones and Collins (3, 4), reported 6 cases of stricture of the sigmoid and 1 of the small intestine after irradiation therapy of carcinoma of the uterus.

In 1935, Newell and Crossen (5) reported 5 cases

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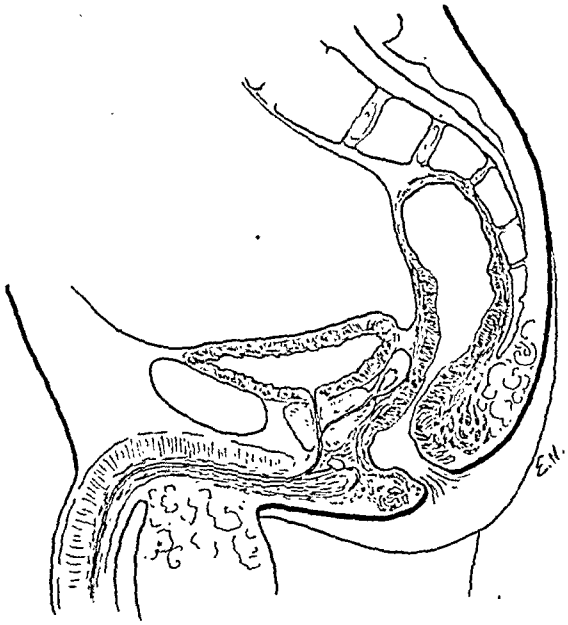


Fig. 1. Diagrammatic drawing showing the site of rectal stenosis following cross fire roentgen therapy for carcinoma of the prostate and bladder.

of rectal stricture after radium and roentgen irradiation for carcinoma of the cervix. The strictures appeared as long as 2 years after therapy and were all easily treated by dilatation. They state that they "have come to expect considerable rectal irritation in the effective irradiation treatment of carcinoma of the cervix, the rectal mucosa apparently being more susceptible to the effect than the bladder mucosa. Ordinarily the rectal irritation subsides after 2-3 weeks. In some instances, however, the rectal irritation progresses to ulceration and infiltration with subsequent stricture formation." Other authors have also mentioned the rectal disturbances associated with irradiation therapy for uterine cancer (6, 7).

David and Lauer (8), in 1932, reported a case of rectal stricture following irradiation treatment of carcinoma of the prostate and David (9) later reported on burns of the rectum following radium applications for carcinoma of the rectum and prostate. Bothe (10) mentioned variable bowel symptoms ranging from mild to severe diarrhea following roentgen therapy in cases of bladder tumors.

It is the purpose of this paper to describe the types of irradiation reaction observed in the rectum, to emphasize that they are not due to a recurrence or an extension of the malignancy, to detail their clinical course and to suggest methods of treatment.

IRRADIATION REACTION IN THE RECTUM FOLLOWING ROENTGEN IRRADIATION FOR CARCINOMA OF THE PROSTATE AND BLADDER

Two patients were observed following intense irradiation, one for carcinoma of the bladder and the other for carcinoma of the prostate. In both cases, several series of cross fire roentgen-ray treatment were given through multiple ports, both anteriorly and posteriorly. In both patients there developed a browny edema of the skin with pigmentation, and during the period of treatment there were intermittent attacks of diarrhea. The patient with bladder carcinoma began to develop intense tenesmus with the passage of blood and mucus about 6 months after his first treatment. When first seen 9 months later he had practically no control of his bowel movements. Similar symptoms appeared in the other patient, except that incontinence did not occur. Both were troubled by painful, almost prostrating spasms of the colon at the time of bowel movements, especially following bouts of temporary fecal impaction, at which times rectal bleeding and irritation became more marked.

The findings on examination were somewhat alike in both cases. Beginning about 5 cm. from the anal orifice, the rectum was narrowed to a diameter of about 1 cm. (Fig. 1). The introduction of the finger into the rectum, even with the utmost gentleness, was painful. The rectal wall felt uniformly thick and indurated but not woodeny hard. The stenosis was due to a contraction of the entire rectal wall. In the patient with the most severe symptoms, there was at first noted a longitudinal ulceration with a gray indolent base. The ulcer healed slowly during the period of several months' observation, and with its healing the marked tenesmus and fecal incontinence became less prominent. The mucosa of the other patient was pale and thin. This patient died of uremia due to a carci-



Fig. 2. Specimen following roentgen treatment for carcinoma of the prostate. Note the localized area of stenosis and thickening of the rectal wall in the lower rectum. Case 2.

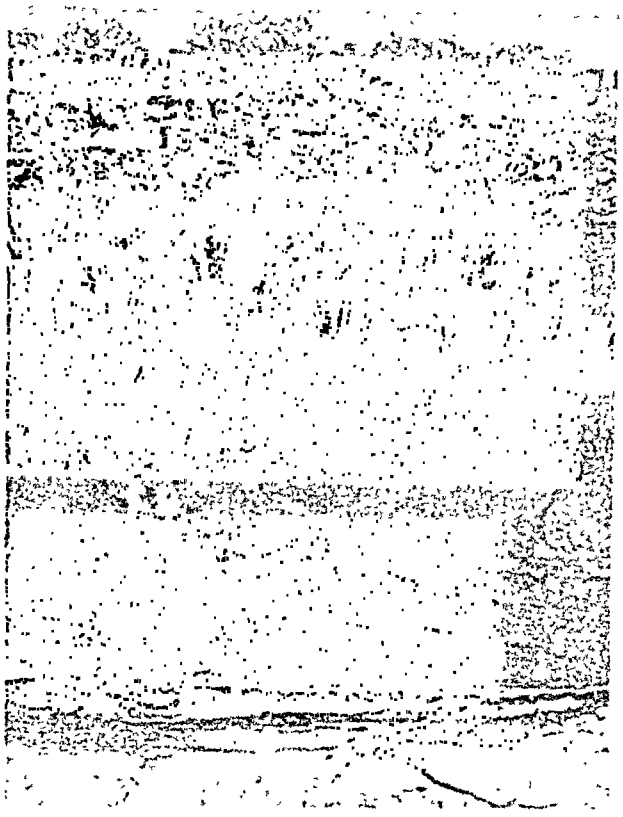


Fig. 3. Cross section of the rectum through the area of rectal stenosis, showing marked atrophy of the rectal mucosa with a slight degree of fibrosis in the sub-mucosa and muscularis. The chief thickness of the bowel wall and the probable cause of the stenosis is marked degeneration with swelling and edema in the muscular coats, especially the circular muscle. Case 2.

nomatous obstruction of the ureters. He was found to have a stenosis of the rectum about 5cm. long due to a marked thickening of the rectal wall involving its entire circumference; the rectum was not involved in the carcinomatous process. Sections of the gut at the stenotic area showed a marked atrophy of the mucosa and a relatively slight amount of fibrosis. The thickness of the rectal wall was largely due to a marked degeneration of the inner circular muscle with swelling of the muscle fibers and edema. The outer longitudinal layer showed definite hypertrophy (Figs. 2, 3, 4).

The symptoms of these patients can be easily understood when the lesion is once recognized. The ampulla of the rectum is practically obliterated by the rectal stenosis, making frequency of movements. The irritability of the rectum produces marked spasm of the bowel with excessive mucus secretion. Bleeding is due to the trauma of the stool passage through the stenotic area and over the intensely hyperemic and thickened bowel wall.

The treatment of these patients is difficult. In both cases colostomy was suggested as a method of relieving the distressing symptoms. Because of local recurrence this was refused. Improvement in the symptoms was obtained by the careful regulation of the diet, with the administration of mineral oil, bismuth subcarbonate and charcoal.

Case I. F. C. A., male, 64 years. In March, 1935, the patient developed hematuria. On cystoscopic examination, a papillomatous carcinoma of the bladder was found. He was given a series of roentgen ray treatments from April 4 to May 13, 1935, the dosage of which was not known to us.

Roentgen Irradiation: First series, begun June 8, 1935, when the patient was transferred to the University Hospital: 165 Kv, 15 Ma, with a thorneus filter equivalent to 2 mm. Cu. at 50 cm. T.S. distance. About 200 r were given through five 15 x 15 cm. portals, two iliac, two gluteal and one perineal. The patient received about 2000 r x 4, plus 1000 r into the perineum in 46 days.

Second series, begun October 8, 1935: the same physical factors were used. The patient received 2000 r x 5 in 60 days through portals as outlined above. In addition, two 8 x 10 cm. portals below the gluteal portals received 2000 r x 2 in 12 days. The last treatment was given on December 31, 1935.

October, 1935: The patient began to have urgency and frequency of bowel movements. In the spring of 1936, his rectal symptoms became much worse, with frequency of movements containing blood and mucus.

July 8, 1936: the remaining bladder tumor was removed by electrocoagulation.

September, 1936: patient examined for the first time; he had practically complete incontinence and constant urgency. The bowel wall was found to be thick and hyperemic. Along the lateral and anterior wall on the right side, there was a long narrow ulceration which had a grayish indolent base. Bleeding occurred on slightest trauma. The proctoscope could be advanced for about 10 cm. from the external orifice.

November, 1936: patient very much improved. On occasions he developed fecal impaction with marked spasm. The lumen was contracted to about 1 cm. at a point beginning about 6 cm. from the external orifice. The ulcera-



Fig. 4. Section from the rectum about two inches above the area of stenosis. The bowel wall is of normal thickness for comparison with Fig. 3. Case 2.

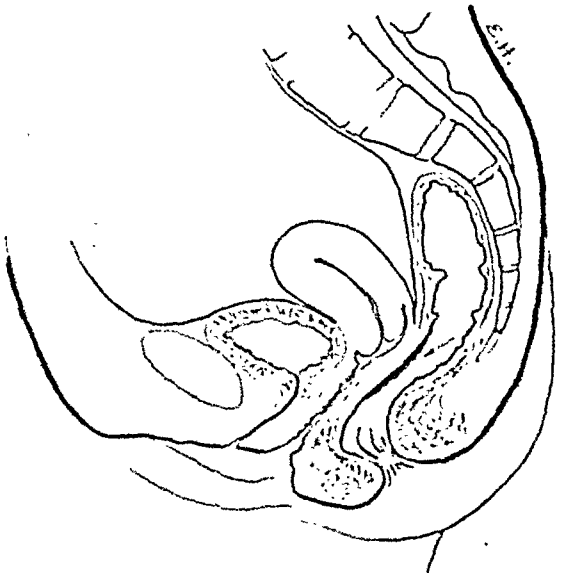


Fig. 5. Diagrammatic drawing to show site of localized proctitis following radium and roentgen irradiation for carcinoma of the cervix.

tion appeared to be covered with granulation tissue. The mucosa was red and thick and bled easily on slight trauma.

April, 1937: patient was having 8-10 bowel movements daily; and there was considerable blood and mucus in the stools, especially if the fecal material was formed. The bowel movements were associated with prostrating spasms of abdominal and pelvic pain. Examination showed definite annular stricture about 1 cm. in diameter and about 2 cm. long in the lower rectum. Colectomy was recommended but refused because of bladder recurrence.

Case II. M. J. M., male, 69 years. *Carcinoma of the prostate.*

Roentgen Therapy: First series, begun August 20, 1934: high voltage radiation, 165 Kv, 15 Ma, filters 0.5 cm. Cu. plus 2 mm. Al, 50 cm. T.S. distance. The radiation was directed through 4 portals measuring 15 x 15 cm., two iliac and two gluteal; 165 r were given per day. The patient received about 1650 r to each skin portal in 30 days.

Second series, begun December 21, 1934: the same physical factors were employed except that 2 mm. Cu. were used instead of 0.5 mm. About 2000 r were delivered in each of four portals in 33 days.

Third series, begun May 13, 1935: the same physical factors except a thoraeous filter equivalent was used instead of the 2 mm. Cu. The patient received 1500 r through a sacral portal and 2250 r through a peroneal portal in 11 days.

October 22, 1935: prostatic resection.

Fourth series, begun December 26, 1935: high voltage radiation using 200 Kv; all other factors as above. The patient was treated through one suprapubic and two gluteal portals, 2000 r being delivered through each portal in 21 days.

August 19, 1936: patient complained of marked tenesmus and rectal bleeding with bouts of constipation and extreme pelvic pain. On examination, the lower rectum was found to be contracted to a diameter of about 1 cm. The bowel wall was thick and indurated, the mucosa smooth and hyperemic. Capillary bleeding occurred on the slightest trauma.

April, 1937: gradual improvement with regulation of the diet. Still had recurrent attacks of fecal impaction with symptoms of intestinal obstruction. The mucosa was pale: the bowel constriction was still present.

April, 1937: death from pyonephrosis with complete block of the ureters by carcinoma. The rectum showed a definite area of stenosis about 5 cm. long; the lumen was contracted to about 1 cm. There was no involvement of the rectum by the carcinoma. The stenosis was due to a marked thickening and contracture of the bowel wall which was found on microscopic section to be due to a degeneration and edema of the inner circular muscle and a definite hypertrophy of the outer longitudinal muscle. The mucosa was atrophic; there was relatively little fibrosis in the bowel wall.

REACTIONS IN THE RECTUM FOLLOWING RADIUM AND ROENTGEN IRRADIATION FOR MALIGNANCY OF THE CERVIX AND UTERUS

Six patients have been observed with rectal lesions following radiation therapy for malignancy of the cervix and uterus. The usual treatment was the implantation of radium in the cervical canal and against the cervix and in a colpostat around the cervix, followed by cross fire roentgen irradiation through multiple ports, both anteriorly and posteriorly, in one to three series. Most of these patients developed temporary rectal irritation which subsided a few weeks after therapy. In five of the six cases there is no evidence of recurrence of the carcinoma.

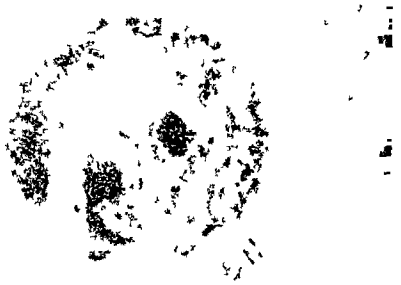
The symptoms of the secondary irradiation reaction were similar in all cases, and appeared from 3 months to 2 years after the radium treatment. Diarrhea, rectal bleeding, rectal pain and tenesmus were the usual symptoms. The diarrhea was not of the usual type, but was characterized by one soft or formed movement in the morning followed by several liquid evacuations containing little fecal matter. There were often 8 to 10 stools per day. Bleeding from the rectum was the most alarming symptom to the patients. It appeared not only at the time of stool but there often followed, an hour or two later, an evacuation consisting largely of blood clots.

The findings on examination were of two types. The first type is characterized by a localized area of in-



Fig. 6. Biopsy from area of acute proctitis, Case 5. Note marked mucous degeneration of the rectal glands, round cell infiltration with hyperemia and edema of the tissue of the rectal wall.

tense hyperemia and swelling of the anterior rectal wall about 6-7 cm. long, corresponding to the position of the cervix (Figs. 5, 6). The rectal mucosa appears normal both above and below the area. Bleeding which was produced by the slightest trauma appeared to be a diffuse capillary hemorrhage and is so profuse as to obscure the field of examination and to produce clots in the rectal lumen.





Figs. 7 and 8. Ulceration of the rectal mucosa following radium and roentgen irradiation therapy for carcinoma of the cervix, Case 7. Note shallow ulcers with indurated base, 6 months after last roentgen treatment and 1 year after radium applications. Fig. 8: 3 months later; ulcers healed with scar formation and telangiectasis.

When observed over a period of 6-8 months, the swelling and hyperemia gradually decreases, and the rectal irritability gradually subsides. There is an exacerbation of the symptoms if the patient becomes constipated or strains at stool.

The second type of irradiation reaction is characterized in the same way by a localization of the rectal lesion to the anterior wall underneath the cervix. The mucous membrane is thin, pale, smooth and atrophic. It is marked by shallow ulcerations, the bases of which are dull gray in color, having much the appearance of a pseudomembrane (Figs. 7, 8). There is no heaping up of tissue at the edge of the ulcer. Dotted over the unwrinkled mucosa are numerous telangectatic vessels which seemed to lie almost on the surface of the bowel mucosa. From these vessels bleeding occurs in considerable amounts on the slightest trauma.

Two patients with radium ulcerations have been observed over a period of months. In both cases the ulcers have healed, in one patient in a period of 3 months, in the other in 10 months. Fibrous scars dotted with telangiectases have remained.

The treatment in these cases was designed to reduce to a minimum all irritation to the rectum. As experience was gained it was found that the irritability of the rectum gradually decreased and only bleeding remained as a prominent symptom. The use of a smooth diet with bismuth subcarbonate and powdered charcoal by mouth were found to be helpful. Mineral oil was given in quantities sufficient to keep the movements soft. Astringent and cleansing enemas were employed but were discontinued when it was found that the above course of therapy was successful.

Case III. E. H., female, 42 years. Carcinoma of the cervix, cervicofundal type. Supravaginal hysterectomy was performed March 12, 1936.

Radium Irradiation: March 30, 1936: 100 mg. radium in cervix with 1 mm. platinum and 2 mm. rubber for 24 hours. 100 mg. radium with 2 mm. platinum and 1 cm. rubber in colpostat intravaginally for 24 hours.

Roentgen Irradiation: High voltage radiation, 200 Kv, 15 Ma, 0.5 mm. Cu. and 2 mm. Al, 50 cm. T.S. distance employed. Radiation directed through 15 x 15 cm. portals, two iliac and two gluteal. The patient received about 300 r daily through 1 portal each day. About 1600 r was delivered in each of four portals in a period of 29 days ending on July 7, 1936.

During the X-ray treatments the patient began to have some rectal irritation and in July her stools became smaller in caliber. In September, she complained of frequent stools, 7-8 daily, often containing fresh blood or clots. On examination, there was an area of edema and hyperemia of the anterior rectal wall underneath the cervix. Oozing occurred from this area on the slightest trauma. There were no other rectal lesions.

November, 1936: patient complained of intense griping abdominal pains with 6 movements daily. Rectal bleeding less.

April, 1937: patient becoming weaker due to metastasis to the lungs. Bowel symptoms somewhat improved. A recto-vaginal fistula has developed.

Case IV. H. B. W., female, 52 years. Sarcoma of the cervix. Biopsy January 5, 1935.

Radium Irradiation: 100 mg. with 2 mm. platinum and 1 cm. rubber in the vagina in a colpostat for 21 hours.

Roentgen Therapy: First series, January 11 to February 8, 1935: high voltage radiation, 165 Kv, 15 Ma, 0.5 mm. Cu. plus 2 mm. Al. Four 15 x 15 cm. portals, two anterior and two posterior pelvic. 200 r per day; total of 1600 r in each of 4 portals.

Second series, April 8 to 20, 1935: same physical factors and 200 r per day; total of 1600 r in one anterior portal and 1600 r in each of two gluteal portals.

Third series, November 2 to 29, 1935: same physical

factors except a thoraeus filter equivalent to 2 mm. Cu. was used instead of the 0.5 mm. of Cu. 200 r per day; 2000 r to each of two iliac and two gluteal portals.

Fourth series, May 2 to 29, 1936: same physical factors except that 200 Kv. were used. 300 r given daily; 2000 r in each of two iliac and two gluteal portals.

Following the last series of X-rays the patient had rather marked cystitis with dysuria. This gradually cleared up.

October, 1936: patient first noted rectal bleeding which became more profuse. She often passed clots after her bowel movement. There was marked rectal tenesmus.

January, 1936: rectal symptoms as above. Examination showed a localized area of hyperemia and swelling in the anterior rectal wall underneath the cervix. Diffuse bleeding occurred from this area. There were no other proctoscopic findings. Diet regulation plus the use of mineral oil, bismuth subcarbonate and charcoal was the treatment recommended.

May, 1937: patient saw bleeding on irregular occasions. No clots noted. On examination, the area of hyperemia and edema was much less definite, although still easily demonstrated. Bleeding was easily induced by slight trauma.

Case V. J. S., female, 41 years. Dilatation and curettage with a diagnosis of functional uterine bleeding, January 12, 1935. Tissue obtained was diagnosed as "questionable malignancy."

Radium: 50 mg. with 1 mm. platinum and 2 mm. rubber inserted into the uterine cavity for 6 hours.

February 7, 1935: biopsy of the cervix.

Radium: 100 mg. with 1 mm. platinum and 2 mm. rubber at the cervix. 100 mm. radium with 2 mm. platinum and 1 cm. rubber in colpostat in the vagina for 24 hours.

Roentgen Irradiation: First series, begun March 13, 1935: high voltage radiation, 165 Kv, 15 Ma, 0.5 mm. Cu. plus 2 mm. Al, 50 cm. T.S. distance employed. Radiation directed through one 20 x 20 cm. anterior portal and two 15 x 15 cm. gluteal portals, treating one portal with 200 r daily. Total of 1600 r were delivered in each of the three portals in 22 days.

Second series, begun June 17, 1935: same physical factors as above. 200 r given daily, using one anterior and one posterior pelvic portal; 1600 r given to each portal in 18 days.

February, 1936: patient began to have rectal pain and bleeding. On examination, there was found a marked thickness of the rectovaginal septum. The rectum contained fresh blood and clots. On inspection of the rectal wall, there was marked hyperemia and swelling of the mucosa with diffuse oozing. Biopsy specimen removed from this area was reported as inflammatory tissue. There was no evidence of carcinoma. This patient continued to bleed from the bowel and was finally admitted to the medical ward for treatment of her secondary anemia.

October 26, 1936: an exploratory laparotomy was performed and no lesion of the large bowel was found to account for the bleeding.

March, 1937: patient still had occasional bleeding from the bowel. On inspection, the bleeding was seen to come from a localized area of the anterior rectal wall underneath the cervix. The hyperemia was less marked than noted before.

Case VI. L. P., female, 55 years. Carcinoma of the body of the uterus extending into the left broad ligament.

Roentgen Therapy, summer of 1932: 6 treatments, amount unknown.

Radium: September, 1932: 2400 mg. hours r into the uterus. March, 1933: 1200 mg. hours r into the uterus. July, 1934: 2400 mg. hours r into the uterus with 1 mm. platinum and 1 mm. rubber.

Roentgen Therapy: July 20, 1934: high voltage radiation, 165 Kv, 15 Ma, 0.5 mm. Cu. plus 2 mm. Al Filtration, 50 cm. T.S. distance employed. Through two iliac and two gluteal 15 x 15 cm. portals, 150 r were given daily until 1600 r was delivered in each of four portals during 27 days.

January, 1936: patient began to note bleeding from the bowel, usually not associated with the bowel movements which she had habitually in the morning but in the afternoon when the movement would consist of clots of blood with little or no feces. She was troubled frequently with abdominal distention.

April, 1936: proctoscopic examination showed the bowel wall thickened and the mucosa hyperemic along the sacral curve of the rectum about 10 cm. above the external orifice. The lumen was contracted to about half the normal diameter and bleeding occurred on slight trauma. Barium enema showed a lack of haustral markings indicating an irritable colon. The patient was advised as to regulation of diet and given charcoal, bismuth subcarbonate and a mild cathartic.

October, 1936: the patient had had very slight bleeding from the bowel occasionally. The lumen was much increased; hyperemia was less.

April, 1937: slight bleeding noted once or twice a month. No other symptoms; proctoscopic picture showed little change.

Case VII. J. R., female, 42 years. Carcinoma of the cervix involving the posterior lip.

Radium, May 16, 1935: 100 mg. radium filtered with 1 mm. platinum and 2 mm. rubber held with a stitch against the posterior lip of the cervix. 100 mg. radium filtered with 2 mm. platinum and 1 cm. rubber in colpostat in the vagina. Irradiation applied for 24 hours.

Roentgen Irradiation: First series, begun June 19, 1935: high voltage radiation, 165 Kv, 15 Ma, 0.5 mm. Cu. plus 2 mm. Al, 50 cm. T.S. distance employed. The patient was treated through two iliac and two gluteal 15 x 15 cm. portals. 200 r were given daily; a total of 1800 r was delivered in each of four portals during 35 days.

Second series, begun November 4, 1935: same physical factors using thoraeus filter instead of 0.5 mm. Cu. Same portals treated until 2000 r x 4 were delivered in 43 days.

April, 1936: the patient developed marked diarrhea with 10-12 movements daily.

May, 1936: the diarrhea was associated with marked bleeding and passage of clots.

June, 1936: diarrhea and bleeding continued with increasing tenesmus and soreness and burning in the rectum after movements. On examination, in the anterior rectal wall underneath the cervix the mucosa was pale and thin and was dotted with several small sharply defined ulcers. Telangiectatic vessels were seen on the surface of the mucosa. The rectum elsewhere appeared normal except for a slight paleness of the mucosa. Barium enema showed irritability of the colon, especially of the rectum and sigmoid. A smooth diet was prescribed for the patient, and mineral oil, bismuth, subcarbonate and charcoal were given.

August, 1936: patient had only occasional slight bleeding. She noticed considerable tenesmus if she ate fruits and other rough foods. The ulcers of the bowel wall now practically healed with definite linear scars. Telangiectatic vessels were numerous.

November, 1936: patient noted only a few drops of blood with bowel movements occasionally. She had no symptoms if she remained on a smooth diet. The ulcers entirely healed but the scars were still visible. Telangiectasis was marked.

Case VIII. A. U., female, 60 years. Epithelioma of cervix involving cervix, posterior vaginal wall and both parametria.

Radium, January 20, 1933: 50 mg. radium with 1 mm. platinum and 1 mm. rubber sutured across the cervix. 100 mg. radium with 2 mm. platinum and 1 cm. rubber in

colpostat in vagina on each side of the cervix. Irradiation for 21 hours.

Roentgen Therapy: First series, begun December 18, 1933: high voltage radiation, 165 Kv, 15 Ma, 0.5 mm. Cu. plus 2 mm. Al, 50 cm. T.S. distance employed. The patient was treated through two iliac and two gluteal 15 x 15 cm. portals. About 150 r were given daily until 1800 r were delivered in each portal during 30 days.

Second series, begun March 10, 1934: same physical factors. One 20 x 20 cm. anterior portal and two 15 x 15 cm. gluteal portals employed; 1600 r were given in each portal during 28 days.

January, 1935: patient began to have 8-10 movements daily, with marked tenesmus. There was some bleeding from the bowel but the patient was more troubled by the passage of clots some hours after a normal bowel movement.

April, 1935: the same symptoms continued. On examination, the lumen of the bowel was filled with dark blood and clots. The bleeding appeared to come from a localized area on the anterior rectal wall. In this area the mucosa was thin and atrophic. There were several small shallow ulcerations. Barium enema showed nothing except slight irritability of the lower bowel. The patient was instructed as to regulation of the diet and given mineral oil, bismuth subcarbonate and charcoal.

August, 1935: the bleeding had continued but was much less than before. The rectal irritability had disappeared. The ulcers were healing and multiple telangiectatic vessels were seen in the thin mucosa.

February, 1936: bleeding only on rare occasions when the patient was constipated. The ulcers were entirely healed. Telangiectatic vessels were more marked in the mucosa.

May, 1937: patient still noted an occasional show of blood if rough foods were eaten. No other symptoms: the bowel ulcerations were completely healed.

DISCUSSION AND SUMMARY

From a study of these cases, several points of interest to the gastro-enterologist and the proctologist may be noted.

1. Irradiation therapy for malignancy of pelvic organs may produce marked secondary effects in the rectum.

2. The rectal lesions produced by intensive cross fire roentgen irradiation are characterized by a progressive constriction of the bowel lumen. The reaction appears to involve all of the layers of the rectal wall. The mucosa may show the intense hyperemia and ulceration of an acute proctitis or may later become thin and atrophic. The symptomatology is due to a combination of marked irritability and stenosis of the rectum, producing tenesmus and frequency of movements, mucus and blood in the stools, spasms of rectal and abdominal pain and bouts of fecal impaction above the rectal stricture.

3. The rectal lesions found after radium and roentgen treatment of malignancy of the cervix are probably largely due to the radium irradiation. The lesion is confined to a well-defined area of the anterior rectal wall beneath the cervix, and varies from an intense hyperemia of the mucosa, with swelling of the rectal wall, to a marked mucosal atrophy, with ulcerations and telangiectases. The symptoms of the acute phase of the irradiation reaction are those of an intense proctitis with frequency of movements, tenesmus, burning pain in the rectum and profuse bleeding during and after movements. As the reaction subsides, the symptoms decrease until occasional bleeding from trauma to telangiectatic vessels is the only remaining complaint.

4. The symptoms of the secondary irradiation in the rectum may not appear for 3-18 months after the last irradiation treatment.

5. The irradiation reaction tends to subside spontaneously if irradiation therapy is discontinued.

6. The treatment of most benefit is one in which trauma to the area of reaction is prevented by insuring soft and non-irritating fecal discharges. In patients with a rectal stenosis, rectal dilatation or colostomy should be considered.

7. It is important to remember the possibility of these reactions. The diagnosis can readily be made on the basis of the history and the proctoscopic findings.

8. The irradiation reaction should not be mistaken for an extension or recurrence of the malignant process.

I wish to thank Drs. Floyd E. Keene, Eugene P. Pendergrass, T. Grier Miller and Albert E. Bothe for the privilege of seeing and reporting their cases.

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DISCUSSION

DR. JEROME M. LYNCH (New York, N. Y.): This very interesting paper of Dr. Ferguson's illustrates something, the fact that I think the patients who are having surgical irradiation should be told what they may expect.

I know of two very prominent medical men who recently told me their mothers had had cervical irradiation and they were sure, from the suffering they underwent, they would have preferred surgery even though it wasn't as curative as radiation.

Radiation appears to be the accepted method of treating cervical carcinomata. The percentages of five-year cures are larger than with surgical extirpation, we are told; however, there is another side to the picture. Experts admit that distressing and painful sequelae frequently occur in neighboring organs. It is with these mishaps that we are forced to cope.

Let us, therefore, consider their origin. Some are due to faulty technic or overdosage but most are the inevitable result of a radium barrage sufficiently powerful to destroy the growth. That is to say, the radiologist has fully considered the damage to neighboring viscera which must result from an adequate radiation of the tumor and has felt that its destruction more than compensates for their impairment. Throughout the world search for the happy medium continues but progress is distressingly slow.

The effects of radiation are the same throughout the body. Smaller doses stimulate and larger ones destroy. Certain cells are more radiosensitive than others; that is, more easily stimulated or destroyed. It is on this basis that the treatment of carcinoma by radiation rests. The more embryological or undifferentiated a cell is, the more

radiosensitive. Hence, in Utopia it will be possible to deliver a barrage sufficient to destroy malignant cells without even stimulating physiology, but here we must accept stimulation of normal tissues in varying degrees.

The immediate result of stimulating tissue is to produce an active hyperemia. In the rectum this may disclose itself by symptoms varying from a feeling of fullness in the ampulla to an actual extravasation of blood. Hemorrhoids, if present, may evince symptoms, and thromboses are frequent, but this is transient and rarely necessitates treatment.

The second state occurs when the stimulation is removed. The pendulum swings the other way. Hypoemia supervenes. The vessels exhibit endarteritis, which appears to be progressive throughout the life of the patient. The resultant poor blood supply causes the tissues to undergo fibrous degeneration. This may continue to stricture formation, and I think very often does.

These structures were the first signs to call our attention to the sequelae of cervical radiation upon the lower bowel. We regret to say that we have had to perform abdominal colostomies upon several patients for this condition, that is, stricture, and Dr. Ferguson spoke of dilatation. That is a very dangerous procedure because, as you know, the bowel always ruptures in the long axis of the gut and you never can tell when you are overdilating, and a colectomy is inevitable, after all, and might as well be done in the first place.

As surgeons of the lower bowel, it is not our province to discuss the treatment of cervical cancer, but our duty to point to the all too frequent reaction of cervical radiation on the rectum. I have on several occasions had to remove the rectum, though we knew it wasn't recurrence of the carcinoma but was done to relieve the pain, and it did that, and we have had to do this also after radiation in rectal cancer.

DR. JAMES T. PILCHER (Brooklyn, N. Y.): You will appreciate the fact that Dr. Ferguson has again given us the pleasure of listening to a very practical presentation of a very difficult subject.

I have had several instances of this complication occur and they are certainly most troublesome in their treatment, and I think if nothing else is brought to our attention by this very excellent presentation, it is the universal use and indiscriminate application of radium, which is so easily purchased from commercial laboratories and employed and utilized by men who know absolutely nothing about the complications and sequelae that may follow its improper application, without a proper attempt to guard against the direct ray on the anterior wall of the rectum.

I agree both with Dr. Ferguson and Dr. Lynch relative to the subsequent treatment in that primarily one should perform a colostomy. Do not wait. You have got to perform it anyhow eventually, and in many of these cases where the lesion has proceeded to a condition of sclerosis, you will have to remove the rectum, which is the only way that this intolerable distress can be controlled.

DR. ROBERT ELMAN (St. Louis, Mo.): I wish to report on one patient who several months after pelvic radiation developed manifestations of acute intestinal obstruction with marked abdominal distention and inability to pass stool. Characteristic rectal changes were observed but there was also definite occlusion due to the inflammatory process; however, with conservative non-operative therapy, continuous gastric suction, nothing by mouth, and enemas, the acute obstruction subsided and, in accordance with the experience of Dr. Ferguson, the acute inflammatory lesion subsided.

DR. V. C. ROWLAND (Cleveland, Ohio): I should like to ask if the speaker has had any cases of gas bacillus infection that seemed to have gained entrance through the irradiated uterus.

I had an autopsied case in which edema developed over the pubes and hypogastrium one year after apparent cure of carcinoma of the uterus by radium. This edema was present about two weeks when X-ray treatments were given on the suspicion of recurrence of carcinoma. There was a rapid generalization of the gas bacillus infection and at autopsy cultures were positive and typical gas cavities in the brain and elsewhere were demonstrated. There was severe proctitis with edematous swelling throughout the pelvis but absolutely no evidence histologically of carcinoma. The pathological opinion at the time was that the local lesions had provided an antrium of infection to the gas bacillus.

DR. J. ARNOLD BARGEN (Rochester, Minn.): I think Dr. Ferguson should be congratulated for bringing this important subject to our attention and that the Committee and Council should be congratulated for offering him the prize for this well presented paper.

Fortunately, these lesions are not common but they often present a very distressing situation.

At the clinic, we occasionally see patients who present such a characteristic picture that we have been designating the disease as "factitial" proctitis and colitis. When we speak of a factitial lesion, we are thinking of a lesion which occurred after irradiation therapy.

The important points about the diagnosis is the situation of the lesion and its very characteristic appearance. Telangiectasia about the lesion is very striking. Differentiation of this lesion and other conditions, particularly neoplasms, is important. The diffuse involvement brings up the consideration of other hyperplastic lesions.

I have seen these lesions remain the same for several years; then they gradually cleared up and left a peculiar tissue-paper-like stellate scar. The lesions appeared on the anterior wall of the rectum, opposite the point where the radium had been applied.

We have also seen a less advanced lesion, following roentgenologic treatment.

Every once in a while, following deep roentgen therapy, patients have diarrhea which is difficult to control. It is probably a phase of the same type of difficulty as the factitial proctitis. In some cases there may be no visible lesions at all, but an intractable diarrhea may persist for weeks and sometimes for months. Symptomatic treatment will usually suffice.

DR. L. K. FERGUSON (Philadelphia, Pa.) (closing the discussion): I want to thank Drs. Lynch, Bargen, Pilcher, Elman and Rowland, for their discussion of this paper.

With regard to the dilatation which Dr. Lynch mentioned and did not feel was justifiable, I can only say that I have had no experience with dilatation of these strictures. Newell and Crosson stated that in five of their cases they were able to overcome the rectal obstruction by dilatation without the necessity for colostomy. As a matter of fact, in the cases I have seen with stricture, colostomy was indicated in both cases but on account of recurrence, it was not insisted upon. One case has already died, and the other, I think, is going to die.

As far as gas bacillus infection is concerned, I have never seen any cases in which the ulcers have been infected by gas bacillus.

Deficiency States Associated with Gastro-Intestinal Disease*

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IN spite of the widespread publicity given to vitamins and deficiency diseases in both the medical and lay press it is not apparent that such clearly recognizable forms of deficiency as beriberi, pellagra, scurvy and xerophthalmia are encountered now with greater frequency than in the past. Even as a result of the economic hardships recently suffered by large sections of the population there has not been a material increase in the incidence of full-blown vitamin deficiency states, at least in the north central portion of this country. However, extensive researches resulting in increased knowledge of the chemical and physiologic activities of some of the vitamins have provided laboratory methods of study which, along with clinical observations, have permitted recognition of early and preclinical states of partial deficiency with increasing frequency.

Such studies have indicated clearly that an abnormal diet is not the only factor responsible for the development of a deficiency disease in an otherwise healthy individual. Other significant predisposing factors include an increased requirement for vitamins during periods of rapid growth and increased metabolism, in pregnancy, or in infectious and toxic states; and altered metabolism with respect to a particular vitamin. It is the purpose of this paper to consider another factor, namely, the relation of impaired or altered gastro-intestinal function to the development of deficiency syndromes. So far as our experience at the clinic is concerned, gastro-intestinal disease is the condition most commonly present as an etiologic factor and one which may be operative without respect to the adequacy of the diet.

Since the gastro-intestinal tract is primarily concerned with the digestion and absorption of food, and therefore with the general nutritive state of the individual, it seems quite obvious that a close relationship should exist between alterations in gastro-intestinal function and the occurrence of a deficiency state. In fact, the relationship may be a reciprocal one, for abnormalities in gastro-intestinal structure and function may be the outstanding feature of a deficiency state, not only in the experimental animal, but also in man. For some years there have been reports, such as that of Eusterman and O'Leary, in which pellagra was reported to be associated with and apparently secondary to lesions involving the gastro-intestinal organs. Three years ago Strauss aroused much interest among those especially concerned with gastro-intestinal and nutritional problems by calling attention to the rôle of the gastro-intestinal tract in the conditioning of deficiency diseases and by collecting a variety of illustrative cases from the literature.

Analysis of the means by which alterations in gastro-intestinal function may set the stage for the development of deficiency states reveals a rather large number of mechanisms which differ widely in character. This obviously is to be expected because of the large variety of conditions which may significantly influence gastro-intestinal function and thus lead eventually to an insufficiency or deficiency of an essential substance which the tissues under normal conditions obtain from food. We have attempted a classification of the alterations in digestive function which may predispose to the development of deficiency states, and we will cite cases illustrating some of the various mechanisms involved (Table I).

In presenting a classification it should be emphasized that in some cases it is difficult to evaluate clearly the various etiologic factors involved and to establish definitely the rôle which the gastro-intestinal tract plays in the development of the deficiency state. In some instances the condition may depend only in part, or perhaps not at all, on the associated gastro-intestinal abnormality, the relationship being entirely coincidental. Experience indicates that, fundamentally, the most significant rôles of the gastro-intestinal tract in predisposing to or conditioning deficiency disease have to do with an inadequate intake of food, loss of essential secretions or of food itself, a lack or decreased production of essential endogenous substances, inadequate intestinal absorption and, perhaps, impaired metabolic activity of certain of the digestive organs.

INADEQUATE INTAKE OF FOOD

An inadequate intake of food is usually taken to be the most common cause of a deficiency state. Beriberi, scurvy, pellagra and xerophthalmia, which have occurred so frequently in the past and which are still observed in the Orient but not commonly in this country, are clear-cut examples of the results which follow a long continued inadequate diet.

Economic difficulties, eccentricities, faddism, ignorance, and chronic alcoholism.—These are in this country the commonest causes of an inadequate diet, and clinicians should be on the lookout for deficiency diseases, particularly among patients who may be handicapped in one of these ways. Excellent examples of these conditions are: the multiple neuritis of chronic alcoholics; the occurrence of nutritional abnormalities due to self-managed, weight-reduction diets, which are inadequate in many respects and followed because of fads and ignorance of nutritional requirements; and beriberi following eccentricities of diet, such as occurred in a case we recently observed and in the one reported by Kepler.

Diseases with anorexia, dysphagia, dyspepsia, and pain.—Attention should also be called to those patients

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who, because of some gastro-intestinal complaint, have voluntarily adopted an eccentric diet. Any disease which leads to anorexia, dysphagia, dyspepsia, or pain (particularly when in the abdomen), *may result in a* deficiency disease caused by an inadequate intake of food. This is well illustrated by the following case:

Case 1. Benign esophageal stricture, from ingestion of lye, followed by pellagra (inadequate intake of food). A woman, aged thirty-three years, four months previously had drunk concentrated lye with suicidal intent. She was thereafter able to swallow only small quantities of liquids because of the development of an esophageal stricture. She was markedly emaciated and had lost 44 pounds (20 kg.). The lesions on her hands and face were characteristic of pellagra. During the course of the disease, diarrhea and dementia developed and a fatal bronchopneumonia ensued. Postmortem examination revealed marked cicatricial narrowing of the esophagus.

TABLE 1

Deficiency states associated with various types of gastro-intestinal lesions

Type of Lesion	Deficiency State	Cases
Esophageal stricture (lye)	Pellagra	1
Gastric carcinoma	Pellagra	4
Gastric ulcer	Pellagra	1
Gastric ulcer	Osteoporosis and nutritional edema	1
Gastric syphilis	Pellagra	1
Malfunctioning gastro-enterostomy	Pellagra	1
Malfunctioning gastro-enterostomy	Pellagra and neuritis	1
Bicornal stomach	Macrocytic anemia	1
Duodenal ulcer with obstruction	Pellagra	3
Obstruction of second portion of duodenum	Pellagra	1
Occlusion of duodenum (with ulcerative colitis)	Pellagra and beriberi	1
Cirrhosis of liver (and fibrosis of pancreas)	Pellagra	1
Biliary fistula	Pellagra	1
Extensive metastasis in liver (?); carcinoma; source?	Pellagra	1
Obstructive jaundice	Multiple neuritis	1
Carcinoma of pancreas (with duodenal obstruction)	Pellagra	1
Carcinoma of pancreas	Sprue	1
Calculous pancreatitis	Sprue	1
Acute pancreatitis (with duodenal ulcer and obstruction)	Beriberi	1
Diffuse chronic pancreatitis	Sprue and pellagra	1
Malfunctioning ileac stoma	Pellagra	1
Malfunctioning jejunal stoma (inadequate feeding)	Pellagra	1
Chronic ulcerative colitis	Pellagra	4
Chronic ulcerative colitis	Pellagra and vitamin A deficiency	1
Chronic ulcerative colitis	Pellagra and neuritis	1
Carcinoma of sigmoid	Pellagra	1
Carcinoma of descending colon (with fistula into small bowel)	Pellagra	1
Associated colitis (gastro-enterostomy for duodenal ulcer)	Pellagra	1
Polyposis	Nutritional edema	1

So far as we are able to determine, this is the only clear-cut vitamin deficiency disease due to an esophageal lesion which has been reported in the literature.

Therapeutic dietary inadequacy.—Of much importance from the practical standpoint is the possibility that a diet prescribed by a physician in the treatment of a gastro-intestinal or other disease may be inadequate in essential substances. The frequency with which limited diets are prescribed because of allergic conditions, and such chronic diseases as peptic ulcer, ulcerative colitis, nephritis, and cardiac disease, make possible the development of deficiency states among individuals affected with these diseases who continue on such diets over long periods of time. We have recently observed a case in which pellagra developed following a year's adherence to an elimination diet in an attempt to relieve hay fever and asthma. The occurrence of scurvy among patients receiving dietary treatment for duodenal ulcer, while something of a rarity, is another example of this type of dietary inadequacy. The following case illustrates very effectively the necessity for care in dietary management, particularly for those patients who for various reasons must follow a restricted diet:

Case 2. Bleeding leiomyoma of the stomach; jejunostomy for feeding followed by pellagra. A woman, aged forty-six, had a bleeding leiomyoma of the stomach which could not be removed surgically. Jejunostomy was performed for purposes of feeding and, after three months on jejunal feedings, there developed stomatitis, diarrhea, and characteristic early pellagrous lesions of the hands. On the addition of brewer's yeast, meat and meat juice to the jejunal feedings, the patient gained 15 pounds (6.8 kg.) in six weeks and the oral and cutaneous lesions disappeared.

LOSS OF ESSENTIAL SECRETIONS OR OF FOOD

The second type of gastro-intestinal disturbance which may lead to deficiency disease is loss of essential secretions or of food even though the diet given is adequate in respect to vitamins. Such loss may occur as a result of vomiting, diarrhea, or because of the presence of an external fistula. The peripheral neuritis which accompanies the vomiting of pregnancy, or which may sometimes develop postoperatively, is at least in part the result of loss of food by emesis and a reduced intake of food. An inadequate supply of, or an increased demand for vitamin B_1, such as may occur in pregnancy, may be contributing factors also:

Case 3. Vomiting of pregnancy with polyneuritis* (loss of essential secretions and food). A woman, aged twenty-six, was three months pregnant at the time of admission to the clinic. She had vomited almost daily for ten weeks and had lost about 50 pounds (22.7 kg.). She originally weighed 200 pounds (90.7 kg.). She was drowsy and confused and had visual hallucinations. Examination revealed a mild peripheral neuritis, nystagmus, limitation in ocular rotation and retinal hemorrhages. Ten days later, following an adequate intake of food, vitamin B_1, liver extract and yeast, all of these symptoms had practically disappeared.

Loss of essential substances or food may also occur as a result of diarrhea. Although the characteristic

*Previously reported by Randall and Wagener.

dehydration incidental to loss of fluid and electrolytes during episodes of diarrhea, recently studied by Wakefield and his associates (16), is well known, actual deficiency syndromes are considerably less familiar. Keefer has described a macrocytic anemia, resembling pernicious anemia, in chronic bacillary dysentery, and Boyce and Padget have reported cases in which pellagra was associated with the diarrhea of rectal disease. The rapid changes in the electrolyte content of the blood, which may occur following the establishment of a pancreatic, gastric, or duodenal fistula with loss of these secretions, are actually part of a deficiency state. Similar conditions may also result from loss of food and secretions from an intestinal fistula, as is illustrated in the following case:

Case 4. External ileal fistula with pellagra (loss of feces). A woman, aged twenty-six, came to the clinic with a fistula of the small intestine of nine months' duration which had developed following drainage of an abdominal abscess. The diet had been adequate, at least during the preceding four months. She had lost 37 pounds (16.8 kg.) from an original weight of 115 pounds (52.1 kg.). Lesions characteristic of pellagra were present on her hands. It was estimated that at least half of the intestinal content had been lost through the fistula.

LACK OR DECREASED PRODUCTION OF ESSENTIAL ENDOGENOUS SUBSTANCES

Just as loss of essential dietary substances or food may lead to the development of a deficiency disease, so also may a lack or decreased production of essential endogenous substances produce a similar effect. The importance of this feature in the etiologic consideration of a particular case is, however, much more difficult to evaluate than are some of the factors previously discussed. Nevertheless, the essential rôle of the stomach, liver, pancreas, and small intestine in maintaining a state of normal nutrition has already been established.

Stomach.—A lack or decreased production of the intrinsic factor of Castle by the gastric mucosa may lead to the development of pernicious anemia, now classed by many as a deficiency disease. The following case illustrates very graphically the effect of the apparent lack of this intrinsic factor following resection of the stomach:

Case 5. Gastric resection followed by macrocytic anemia* (lack of intrinsic hematopoietic factor). A woman, aged forty-eight, on admission to the clinic had gastric carcinoma, achlorhydria, and macrocytic hypochromic anemia. Hemoglobin was 50 per cent and erythrocytes numbered 3,600,000 per cubic millimeter of blood. Eleven months after gastric resection the patient returned complaining of stomatitis. At this time the hemoglobin was 54 per cent and erythrocytes numbered 2,600,000 per cubic millimeter. Smears of the blood revealed marked macrocytosis with normochromasia and a right shift of the neutrophils. There was prompt improvement of the blood picture following the administration of liver extract parenterally.

Lack of secretion of hydrochloric acid frequently results in hypochromic or nutritional anemia due to a deficiency in the absorption of iron. There is experimental evidence to suggest that lack of hydrochloric acid may interfere considerably with the absorption of vitamins B, C, and G (B_2) and, as a result of this, or because of excessive destruction of the vitamin, achlorhydria may be a significant predisposing factor in the development of a deficiency state.

Liver.—The influence which the liver may play under these circumstances is best illustrated by those conditions in which there is a loss of bile through a biliary fistula or when bile fails to reach the duodenum in adequate quantities because of congenital atresia or other obstruction to the common duct. Aldrich has recently reported observations of eleven infants in whom the bile duct was found at postmortem to be congenitally atretic. Despite an adequate diet and although clinical evidence of vitamin A deficiency was lacking, the livers of six of the eleven showed microscopic changes similar to those described in vitamin A deficiency by Widdicombe and Howe. We have observed a case of pellagra in association with an external biliary fistula, and McVicar, in 1925, reported a case of peripheral pruritis in which long-continued obstruction of the jaundiced duct to stones in the common duct proved to be the only significant predisposing factor. Recent interest in disturbances in coagulation of the blood of patients with jaundice has been directed toward the possibility of reduction in prothrombin content of the blood as a result of deficiency of certain factors, namely, vitamins C and K. Failure of bile to enter the duodenum may be a possible etiologic factor in such a deficiency, since vitamin K, which is fat soluble, and also vitamin C, may depend in part at least on the presence of bile for absorption.

Pancreas.—The failure of pancreatic juice to enter the duodenum must be an important factor in predisposing to a deficiency state, as is illustrated by the cases we have observed in which pancreatic atrophy, lithiasis, or carcinoma were present:

Case 6. Pancreatic lithiasis with pancreatic insufficiency simulating sprue* (lack of essential constituent; inadequate absorption of fat). A man, aged sixty-five years, complained of diarrhea of four years' duration. His stools were frequent, voluminous and greasy; he was cachectic, and had diabetes mellitus. He had lost 60 pounds (27.2 kg.). His tongue was reddened and its appearance was characteristic of that seen in sprue. Examination of the blood revealed the hemoglobin to be normal; the serum protein was reduced (5.1 gm. per 100 c.c.). Roentgenograms of the stomach, intestines, and colon were negative; that of the pancreas showed multiple areas of calcification. Examination of the duodenal content on two occasions failed to reveal any pancreatic ferments whatever. The fat content of the stool was 21.8 per cent by weight. Careful dietary and medical management did not check the diarrhea or loss of weight, but the patient finally improved remarkably on pancreatic extract. His tongue resumed its normal appearance and most of the lost weight was regained.

Small intestine.—Failure of the small intestine to secrete juice containing adequate amounts of enzymes may be a contributing factor in predisposing to a deficiency disease. In such a case as Case 8 it seems quite likely that the diffuse inflammatory and atrophic change in the stomach and small intestine leading to lack of secretion of certain enzymes may have been a

*Previously reported by Heck and Walters.

*In referring to sprue in this paper, we have reference to a clinical syndrome characterized by stomatitis, fatty stools, emaciation, and disturbances in the metabolism of calcium, with hypocalcemia, osteoporosis, and at times there is also tetany. Hypoproteinemia and edema and frequently macrocytic hypochromic anemia may also be present. This syndrome we have seen in connection with extensive atrophy of the intestinal mucosa, pancreatic insufficiency from carcinoma and atrophy, enterocolic fistula, and in association with tuberculosis of the lymph nodes.

significant factor, along with failure of absorption, in producing the clinical picture of sprue and pellagra.

INADEQUATE INTESTINAL ABSORPTION

The importance of bile, hydrochloric acid, and pancreatic juice in facilitating intestinal absorption and the rôle which the absence of these substances may play in the development of deficiency states has already been emphasized. However, of perhaps equal importance are those changes which may involve the intestine directly and interfere with absorption. Obstruction, atrophy, or other mucosal disease, or short circuiting between loops of intestine or the stomach and colon, are specific changes which may significantly interfere with absorption.

Obstructing lesions.—Many clinicians have observed cases in which obstructing lesions in the stomach or duodenum have led to the development of secondary pellagra. Two of our patients with malfunctioning gastro-enteric anastomoses had pellagra, and one in addition had peripheral neuritis. In three cases of duodenal ulcer with obstruction and in one of cicatricial obstruction of the second portion of the duodenum pellagra was present, whereas in another case duodenal ulcer with obstruction led to the development of a clinical picture of beriberi. In these cases probably other factors, such as reduced intake of food and vomiting, may have hastened the development of the deficiency state, but inadequate absorption as a result of the obstructing lesion and interference with the normal passage of the gastro-intestinal contents were also potent factors.

Case 7. Duodenal ulcer with obstruction and pellagra (inadequate absorption). A man, aged sixty-four, came to the clinic because of attacks of abdominal pain of four or five years' duration. For six months this pain had been associated with periodic vomiting of retained food. There was a characteristic gauntlet-type of pellagrous lesion of the hands and wrists, increasing mental depression and an unexplained diarrhea. Roentgenologic studies revealed duodenal ulcer with obstruction, a finding which was confirmed at operation.

In this connection it is interesting to note that Faber and Meulengracht have reported cases of intestinal stricture with pernicious anemia; failure of absorption of adequate amounts of hematopoietic factor because of the intestinal stricture was considered the underlying predisposing cause by these authors.

Atrophy or disease of the intestine.—It seems quite clear that atrophy or diffuse inflammation of the mucosa of the intestine might seriously interfere with the absorption of adequate amounts of essential nutrient materials from the intestine. Many of the changes accompanying sprue have been explained on the basis of some such failure of absorption. We have omitted from discussion most of the cases of sprue which have been seen at the clinic and reported by one of us (Snell) in which the principal gastro-intestinal changes were demonstrated roentgenologically to be in the small intestine and pathologically to consist of atrophy of the mucosa. The following case, in which diffuse gastro-enteritis seemed to be the only reasonable explanation for the deficiency states which were present, illustrates the effect of diffuse changes in the mucosa in the development of such conditions:

Case 8. Diffuse gastro-enteritis with pellagra and sprue (mechanism of deficiency uncertain; lack of essential secretion? failure of absorption?). A man, aged thirty-seven, had intermittent diarrhea fifteen months before his admission to the clinic. His stools were profuse, frequent, and of the fatty type. On examination, emaciation and dehydration were outstanding, the patient's weight being 82½ pounds (37.4 kg.). His tongue was reddened and its appearance suggested sprue; his hands presented a dermatitis, typically pellagrous in appearance, and the rectal mucosa bled easily. Gastric analysis revealed achlorhydria. Roentgenograms of the stomach were negative; those of the head revealed osteoporosis. The serum calcium was 9.6 mg. per 100 c.c. The stools contained an excess of fat. The patient's course was one of progressive failure, delirium and death. At necropsy the only significant finding was diffuse gastro-enteritis.

Internal fistulas: short circuiting.—Fistulas which short circuit the small intestine entirely or in part are a very interesting but fortunately uncommon cause of deficiency disease. In spite of the fact that the intake of food is adequate, so little of the gastric contents may reach the small intestine that inadequate absorption results. Gastrocolic or duodenocolic fistula, or entero-enterostomy, may be responsible for avitaminosis; there are reports in the literature of several cases in which the clinical picture of sprue had as its pathologic basis a gastrocolic fistula, and we have records of one case in which a latent sprue syndrome was precipitated by gastro-enterostomy. Urmy and his associates have reported a case of beriberi in which all but 20 inches (50.8 cm.) of the small bowel had been sidetracked by entero-enterostomy. We have observed four cases of gastrocolic fistula with associated deficiency states, all of which presented different clinical pictures. In one instance there was nutritional edema alone, and in another edema was associated with tetany and a low serum calcium; in the others, night blindness and a sprue-like syndrome were present.

Case 9. Gastrocolic fistula with nutritional edema and night blindness* (inadequate absorption of vitamin A). A man, aged forty-eight, had undergone gastro-enterostomy for duodenal ulcer sixteen years previously. Eleven years later diarrhea developed and, the following year, night blindness. The patient could see perfectly by day, but at night vision was poor and he was unable to drive his car or to walk without colliding with various objects. His diet had been adequate in every respect. Examination of the eyes revealed no local disease. Moderate edema of the legs was present. Following repair of a gastrocolic fistula, complete recovery resulted and the night blindness disappeared.

In this case of night blindness there was an adequate dietary intake of vitamin A, but because of its failure to reach the small intestine as a result of the gastrocolic fistula it is presumed that inadequate amounts were absorbed.

Case 10. Gastrocolic fistula with sprue (inadequate absorption). A man of forty had undergone gastro-enterostomy for duodenal ulcer five years previously. Eight months prior to his admission to the clinic diarrhea, with five to six watery stools daily, developed. Subsequently, edema of the legs, lower abdominal pain and distention occurred. Examination revealed emaciation, edema of the legs and ascites. He had macrocytic hypochromic anemia. The serum protein was 4.1 gm., and the calcium 7.8 mg. per 100 c.c. Roentgenograms of the bones showed osteoporosis, those of the stomach gastrocolic fistula. Free

*Previously reported by Wilbur and Eusterman.

hydrochloric acid was present in the gastric contents. Jejunostomy was performed for feeding purposes, but death occurred subsequently from perforated gastric ulcer.

This remarkable clinical picture closely resembling sprue was not associated, as is usually the case, with atrophy of the gastric and intestinal mucosa but with a gastrocolic fistula which sidetracked the small intestine, thus interfering with intestinal absorption and leading to a characteristic clinical picture of sprue. Similar cases have been reported by Fairley and Kilmer.

ALTERATIONS IN METABOLISM

Alterations in the metabolic activity of some of the organs of the gastro-intestinal tract may theoretically predispose to the development of a deficiency state. The relationship is not as yet definitely established, however. Since the liver is apparently essential to the conversion of carotene to vitamin A, and since it it such an important storehouse of the vitamin, it is readily conceivable that extensive hepatic damage might lead to deficiency of vitamin A. Such a case was reported by Blegvad, and we have also observed a case of pellagra in which one of the underlying pathologic changes was extensive carcinoma of the liver. It is also quite likely that metabolic activity of the pancreas, and perhaps of the mucosa of the stomach and small intestine, may be significant in conditioning deficiency states under certain circumstances.

One possible rôle by which the gastro-intestinal tract may influence the development of a deficiency disease is that which leads to destruction of the vitamin by bacterial or chemical activity. Practically nothing is known of the clinical significance of such a possibility in man; but there is some evidence to suggest that in animals, certain vitamins are destroyed in large quantities in the gastro-intestinal tract.

Relation of diseases of the colon to deficiency states.—It is surprising how frequently deficiency states may be associated with diseases of the colon, and conversely, how frequently evidence of colonic disease or dysfunction is found in deficiency disease. Mackie has recently reported a group of cases of chronic ulcerative colitis, in 62.6 per cent of which there were symptoms interpreted as evidence of deficiency states. The etiologic relationship of these various factors and the sequence of their development is often impossible to elucidate. Is the ulcerative colitis which is seen in cases of pellagra a secondary or primary condition; or, if it is primary, how does the disease of the colon lead to the development of the deficiency state? It may do so because the diet has been inadequate or because of loss of essential substances or food resulting from the diarrhea, or because of reflex disturbance in function of the stomach or small intestine. We have observed a variety of deficiency states in association with diseases of the colon (Table I).

The difficulties which may arise when one attempts to evaluate the sequence of events in some of the cases is well illustrated by the following report:

Case 11. A man, aged forty-one years, was examined because of diarrhea which he had had intermittently for two years and steadily for eight months. He had been on a somewhat limited diet and had used alcohol in fairly large quantities at intervals during this time. Examination revealed a loss of weight of 40 pounds (18.1 kg.) but was otherwise negative. The stools were watery and cultures and examination failed to show significant organisms or parasites. The rectal mucosa viewed through the proctoscope had the appearance of diffuse proctosigmoiditis. Roentgenologic examination of the colon revealed an atypical form of ulcerative colitis in the sigmoid, transverse colon, cecum and ascending colon, and this was the clinical diagnosis which was made at that time. During the course of dieting and vaccine therapy, stomatitis developed and, three months later, the patient presented the characteristic cutaneous lesions of pellagra and the typical symptoms and findings of multiple neuritis. There was gradual improvement following treatment, with disappearance of the cutaneous and nervous symptoms.

While in light of subsequent developments it seems most likely that the patient's symptoms were due to pellagra following an inadequate intake of food and the use of alcohol, nevertheless, early in the disease, before the development of cutaneous, oral and neurologic changes, the clinical picture resembled that of an atypical chronic ulcerative colitis.

COMMENT

In this paper, in order to be certain of the diagnosis we have limited the discussion to those cases in which the deficiency disease was obvious and clearly recognizable. In so doing we have omitted many cases in which the symptoms of a deficiency syndrome were apparently early and not clear cut. Obviously, in the past, many such cases presenting early or preclinical states of vitamin deficiency have been overlooked or misinterpreted. With the further development of clinical experience and laboratory methods of examination, however, the diagnosis of these early conditions will be made with greater certainty and confidence. It will quite likely be found that the mechanisms by which the gastro-intestinal tract may predispose to such states of mild deficiency are similar to those we have presented.

In the development of deficiency states a large variety of factors may be significant. While the fundamental change is due to a failure in the supply of vitamins or other essential substances to meet the demands of the tissues, this failure or inadequacy may come about as a result of many widely-differing pathologic or physiologic changes. It seems quite likely that many factors other than those which have been mentioned may be significant predisposing causes of deficiency states. Why occasionally in a patient with obstructing pyloric carcinoma pellagra should develop, while in the majority of patients with a similar condition it does not develop although the diet may have been apparently equally limited or the degree of obstruction equally great, cannot as yet be ascertained. The problem seems quite similar to that presented by the failure of most patients with extensive carcinoma of the gastro-intestinal organs who have had a very limited intake of food over a considerable period of time to reveal evidence other than emaciation or cachexia of a deficiency disease. It is also difficult to explain the fact that patients with the same type of lesion, such as a gastrocolic fistula, may exhibit very little evidence of nutritional disturbance, or else may present a variety of deficiency states such as nutritional edema, sprue, night blindness and tetany. Factors such as the antecedent diet, a previous storage of the esential substances, and the size, location and

duration of the fistula, may account for this interesting phenomenon. Doubtless, however, this is not the whole story.

We have also been impressed by the fact that a single deficiency disease, such as pellagra, for example, may be associated with a variety of different gastro-intestinal abnormalities (Table I). The relationship between the pellagra and the associated disease is not always easy to establish; in some cases it seems clear that the pellagra is of the secondary type, whereas in others, the evidence is less definite and a coincidental association is entirely possible.

A review of the material which we have presented reveals that pellagra is by far the most common deficiency disease which we have encountered in association with gastro-intestinal lesions. This is probably best explained by the fact that pellagra is actually one of the most common clinically recognizable deficiency diseases in man, and that the components of the vitamin B complex are most susceptible to the influence of altered gastro-intestinal function. However, the relative ease in recognizing pellagra and the difficulty in recognizing other, less well-known deficiency diseases must be taken into consideration.

One important practical aspect of this problem is the serious prognostic importance of the deficiency diseases in those cases in which a surgical attack on the gastro-intestinal lesion is contemplated. It was our early experience that patients with such complications tolerated major surgical procedures very badly, and in four of the five cases we have reported in which operation was performed after the development of the deficiency disease, death followed soon afterward. In this respect these patients resembled those with uncontrolled Addison's disease or diabetes, in which case any major surgical procedure is very hazardous. Since the unfortunate early surgical results just noted, it has been our experience that, if operation is contemplated, it should be done only after the deficiency state is adequately controlled and treated; under such circumstances the surgical risk is not excessive.

SUMMARY

The rôle of the gastro-intestinal tract in the development of conditioning of deficiency states may be: (1) the result of an inadequate intake of food, due to anorexia or an incomplete diet; (2) the result of a loss of essential secretions or of food, due to vomiting, diarrhea, or external fistulas; (3) the result of a lack or decreased production of essential substances (for example, the hematopoietic factor, bile, or other digestive juices), and (4) the result of inadequate intestinal absorption, due to obstruction, short-circuiting produced by fistulas, and atrophy or disease of the intestinal mucosa.

Pellagra has in our experience been the most commonly observed deficiency disease associated with gastro-intestinal abnormalities. This suggests, and it has been the experience of others, that the components of the vitamin B complex are most susceptible to the influence of altered gastro-intestinal function.

There is as yet no good explanation for the very interesting observations that a single deficiency disease, such as pellagra, for example, may be associated with or produced by a variety of different gastro-intestinal disturbances. On the other hand, several distinct deficiency syndromes may be observed in patients with the same gastro-intestinal lesion.

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DISCUSSION

DR. GEORGE R. COWGILL (New Haven, Conn.): Mr. Chairman and Friends: This paper presents several points worthy of comment. It has taken a long time for clinicians to appreciate the fact that one of the best treatments of many conditions is the maintenance of a proper nutritive state. Of course, this means thinking about foods instead of new and interesting drugs and similar remedies. In his interest in these more novel kinds of treatment the clinicians too often forget the obvious fact that unless the organism is provided with an adequate supply of all of the dietary essentials, it can not recover as the clinician may desire.

The paper just presented summarizes many interesting conditions which quite obviously are due to failure to supply the organism with proper amounts of various dietary essentials, chiefly those in the vitamin group. Assuming that adequate diets were offered, the lesson seems to be that individuals with an abnormal gastro-intestinal tract resulting in surgical treatment of one kind or another may be unable to absorb the requisite amount of administered vitamin.

Considering some of our own recent experiments with dogs, it occurs to me that clinicians ought to consider the possibility that different pictures, different symptom complexes, may be due to the same fundamental cause. Let me illustrate this by citing the behavior of some of our dogs subsisting on diets deficient in vitamin G, or riboflavine, as we should now call it. When the dogs subsist on diets markedly deficient in this factor, they develop a profound collapse after about one hundred and thirty days. This collapse may be treated successfully and with striking results by parenteral administration of the vitamin, the animals recovering sufficiently in about six hours to be able to stand; on the following day they are able to run

around and appear to be normal. On the other hand, when the animals receive as supplement to the basal diet one-half the daily amount of the vitamin found to be adequate for the normal controls, they never exhibit this collapse. They live more than twice as long as the "acute" animals —two hundred and fifty and more days—but they do develop a true ataxia associated with lesions in the posterior columns of the spinal cord. These two conditions, the collapse without ataxia characteristic of the severe and acute deficiency and the ataxia exhibited by the "chronic" animals, are evidently due to the same fundamental cause, namely lack of vitamin G, operating however to a different degree, the acute condition resulting from a marked shortage and the chronic condition from a moderate lack of vitamin maintained over a much longer period. May you not have this situation in many of your clinical cases? May this not serve to explain some of your controversies over the interpretation to be given various symptoms?

With the development of new methods for detecting lack of vitamin B as well as of other vitamins, it should be possible eventually for the clinician to apply these tests and to determine where a state of vitamin subnutrition exists, in which case particular care can be taken to insure that these patients receive sufficient amounts of the vitamins. Clinicians will do well to watch the developments in this field because of their significance in practical work.

It seems pertinent to point out that not all preparations of vitamin B are of equal value in clinical work, particularly if given through a fistula in the large intestine. We have made some observations on dogs provided with a valvular cecostomy and have had occasion to put various vitamin B preparations into the valve. We were quite astonished to find that not all preparations were of equal value. Therefore, if a surgeon wishes to administer vitamin B via a fistula in the large intestine, he should remember that the preparation must be properly selected. Curiously enough, the fullers earth adsorbent used in preparing the present international standard for vitamin B does not readily yield its adsorbed vitamin to the organism. Evidently the conditions in the large intestine do not favor ready elution of the vitamin from the mineral material. It is not unlikely that similar facts will be discovered concerning the other vitamins.

Another practical point occurs to me. If clinicians are to provide these special cases with sufficient amounts of the various vitamins, it is necessary to know about how much of each is required by the individual. If we know, for example, that a normal adult human being needs as a minimum from one to two milligrams of pure vitamin B per day, then, in the face of an abnormal alimentary tract, we can allow for some factor of safety and give many more milligrams in order to allow for wastage due to imperfect absorption. How about the other vitamins? Present indications are that the average person requires at least 3500 international units of vitamin A daily, and probably about one milligram of ribo-flavine (vitamin G) per day. Mere recitation of these figures should suggest to you that we have here a field of knowledge most important to clinicians treating these cases; and if this knowledge is to be properly applied, the clinicians must become familiar with it or else see that some of their colleagues have the requisite information applicable to these particular cases.

How are we to give all of these vitamins? I know that it is clinical heresy to suggest that we should give "mixed remedies" or so-called "shot-gun prescriptions." However, it seems to me that we are perfectly justified in giving these vitamins in the form of mixtures. The Council on Pharmacy and Chemistry of the American Medical Association has ruled definitely against such mixtures of vitamins. If these physiologically important substances were like drugs in their action, then this attitude would certainly be correct. However, the vitamins are essentially foods, and all of them are required. To my mind the only serious argument which can be advanced against the use of mixtures of them is that in such mixtures some of the vitamins may inactivate others, but this is a matter amenable to laboratory and clinical tests, and the results of such tests already at hand do not afford convincing support for the position taken by the Council. Since mixtures of the vitamins are not to be permitted, the clinicians are necessarily forced to give to their patients, who cannot very well handle materials via the alimentary tract, parenteral injections, first of one vitamin, then of another, and so on. This is a most impractical and seemingly unnecessary procedure, especially when suitable mixtures containing at least the daily requirement of all of these essentials can doubtless be provided. When dealing with fundamental food factors instead of drugs, as in this situation, it seems to me that we are justified in subscribing to what is clinical heresy in suggesting that it is proper at times to administer vitamin mixtures in clinical work.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): I was interested in the discussion by our Chairman. The Boston school which he represents has done outstanding work in this field. One point of practical importance to all of us who come in daily contact with patients with gastro-intestinal lesions complicated by deficiency disease is to make sure that those who are obliged to submit to operation have adequate pre-operative preparation. The essayist referred to a contribution by O'Leary and myself published some years ago in which this feature was greatly emphasized. Inadequate preparation presupposes a high surgical mortality.

In the second place, one must always be on the lookout for evidences of deficiency in the conditions cited by Doctor Wilbur. Just before my departure to attend this meeting I saw a young Canadian woman who undoubtedly had an unnecessary gastro-enterostomy for a functional type of dyspeptic complaint. This procedure was followed by a rather persistent diarrhea and achlorhydria. There was adequate pre-operative gastric acidity. In addition to a marked loss in weight she developed a suspicious dermatitis on the dorsum of both hands, which had practically disappeared when she came under our observation. However, on questioning her she stated that she had been treated for pellagra by a competent internist in a neighboring city. Now it is highly essential in this case that before the gastro-enterostomy is taken down, adequate pre-operative preparation with the essential vitamins, etc., should be carried out. The surgical mortality is particularly high in pellagrous types of deficiency disease.

DR. JOHN L. KANTOR (New York, N. Y.): If there is time, Mr. President, I should like to compliment the speaker on his beautiful method of presentation. He followed the old three-way rule of telling his audience what he was going to tell them, then telling them, and then telling them what he told them, so he drove home every point.

The discussion by Dr. Cowgill was all too short in proportion to its importance. He referred to tests for vitamin deficiency. I am not sure how perfect or how clinically effective these are, but such tests should be more generally known by the profession.

The daily requirements of vitamins are again not universally known by the profession, and here also is a field for popularization of the available knowledge.

DR. CHESTER M. JONES (Boston, Mass.): I should like to say that this paper interests me a good deal. It seems to me it is a timely one because of the fact that nowadays we are able to make diagnoses of gross diseases and treat them adequately, but now it come to a point of really bringing about a satisfactory convalescence in many instances, or shortening convalescence, or carrying

on a case of stricture of the esophagus under a long period of undernutrition.

I have jotted down several cases of patients I can recall quite distinctly who bring up the points Dr. Wilbur and Dr. Cowgill have made. One patient had a cancer of the tongue which was resected in part. He was told to limit his diet and did so voluntarily, living on crackers and chocolate ice cream sodas for nearly two years. Then he was sent to me because he was jaundiced, and I was asked whether he had metastases to the liver. He had slight jaundice, his tongue showed a definite stomatitis, and there was a blood picture of pernicious anemia, although there was plenty of acid in his stomach. The admission of adequate amounts of liver by mouth in a very short time restored his blood to normal and caused his jaundice to disappear as well as the stomatitis. That case represents a deficiency due to an inadequate dietary intake.

We see little adult scurvy nowadays, but I recall one patient on an ulcer regime which he maintained for a year beyond the time his physician required it. This patient came in with swollen joints and subsequently developed perifollicular hemorrhages and typical scurvy, due to a deficient diet. The entire clinical picture cleared up rapidly following the administration of orange juice.

Another case suggesting the possibility of sub-vitamin deficiency was that of a youngster with ulcerative colitis and a story of prolonged undernutrition because of his mother's dietary suggestions which amounted to a food fad. This child had skin lesions which were purplish and erythematous, and was generally undernourished. Because he scratched the skin lesions, they became infected, and healed only after a period of months, rather than days as they would normally have done. We suspected a Vitamin C deficiency, though not full-blown scurvy. The Vitamin C content of his blood was low, and he was at once given a Vitamin C concentrate in adequate amounts. With the administration of this specific substance the skin lesions cleared up rapidly.

A fourth patient, with a duodenal ulcer, had a gastro-ileostomy performed by mistake. An ulcer and stricture resulted at the lower end of the ileum. This patient came in with definite signs of a peripheral neuritis, and in addition, was mentally disoriented and difficult to manage. He had definite neurological signs, and the diagnosis was made of a peripheral neuritis and possibly an intracerebral lesion, or beriberi with cerebral manifestations.

A lumbar puncture was performed, and the fluid showed an increased protein content with a cell count of 300 cells per cubic millimeter. At first the neurologist refused to believe it might have been due to dietary deficiency. We found in the literature that beriberi, as reported in the French Colonial literature, occasionally was associated with evidences of meningeal irritation. Vitamin B in this instance cleared up the patient's symptoms, with a return to normal of the spinal fluid.

Another patient presented the rare clinical picture of ulcerative colitis and full-blown Graves' disease. He came to the clinic because of failing vision, and the ophthalmological consultant said that he had an optic neuritis which was definite. There were some signs of peripheral neuritis, which were not so marked as optic neuritis.

We questioned as to whether the optic neuritis was a manifestation of the diet deficiency, but in the first place we successfully treated the Graves' disease by operation, and his ulcerative colitis improved proportionately. At the same time we fed him large amounts of Vitamin B, with almost complete restoration of function of the optic nerve.

I should like to ask Dr. Wilbur whether he has seen a proctoscopic picture similar to that of ulcerative colitis with bleeding following prolonged undernutrition. I recently saw a young woman who apparently presented such a picture. The patient, a girl of 25, had lost 90 pounds in about six months' time by voluntary dietary restriction. She then tried to stop the loss in weight but continued to lose in spite of an apparently adequate diet. During the later months she developed an intractable diarrhea, and by proctoscope had colonic lesions typical of ulcerative colitis. She is at present getting better on adequate diet and intensive vitamin therapy.

Physicians practicing in the South tell me that they do not see intestinal lesions in sprue, but it seems to me that the intestinal lesions in this case might have been due to a deficiency state.

I should like to call attention to the fact familiar to all of us and not too greatly stressed, that the appearance of the tongue is not frequently enough noted. Our forebears always talked about the tongue, but I am not sure they always knew what it meant when they described it. Nowadays there are many changes in the tongue which may be the first symptoms of deficiency disease of the pernicious anemia type, or sprue, or certain other syndromes not so well known. I think its importance can't be too much emphasized.

DR. DWIGHT L. Wilbur (Rochester, Minn.) (closing the discussion): I appreciate the discussion which this paper has received and am glad that, in the discussion, emphasis was placed on some important points in regard to deficiency diseases which I did not have time to mention.

We selected cases in which the deficiency state was very obvious in order that there might be no question as to the diagnosis.

The points Dr. Cowgill brought out are exceedingly important. As yet, not very much advance has been made by clinicians in the recognition of what are called preclinical or early states of vitamin deficiency. In the next ten years we hope great advances will be made in the diagnosis of such conditions with the help of Dr. Cowgill and other investigators who have done so much experimental work in this field.

At the present time very little is known of the actual requirement of man for the various vitamins. Apparently, there are both minimal and optimal requirements. It seems very obvious that in many of the cases we have reported the intake of vitamins was deficient; in other words, the intake of certain vitamins was less than the minimal requirement. There is apparently a wide zone between such a minimal requirement which one would expect to be associated with a clinically recognizable deficiency state and the optimal requirement which one would expect to be associated with a state of excellent health. We do not know how wide this zone actually is nor what its limitations may be, but Dr. Cowgill and other investigators are helping us in elucidating this problem.

The requirement of man for each vitamin probably will best be expressed in future years as are the requirements for protein today, namely, as minimal and optimal requirements.

It is a curious fact, difficult to explain, that most patients who have extensive malignant disease of the gastro-intestinal tract and who live for long periods of time on diets which are obviously inadequate in vitamins fail to show signs of a deficiency state other than emaciation or cachexia.

I think that all of us as clinicians will appreciate the fact that the best way for a patient to secure an adequate supply of vitamins is in the natural state, namely, in foodstuffs. If it seems advisable to supplement foods with vitamin preparations this may easily be done.

Dr. Jordan brought out a very important point in this connection, and I believe it illustrates the attitude that the modern physician should take, namely, to emphasize

to the patient those foods which he should eat rather than to place emphasis, as has been done for generations, on those foods which he should not eat.

Dr. Jones raised the question of disturbance of the colon in relation to deficiency states. In two of our cases we found evidence of chronic ulcerative colitis. What the relationship may be between disease of the colon and deficiency states, in other words, which is primary and which is secondary, is impossible to state in many instances.

The Diarrhea of the Pancreatic Insufficiency*

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THERE are innumerable causes of diarrhea. Many diseases and functional disturbances of the body are associated with this symptom. Often, the cause is some form of intestinal disease, but the cause of a diarrhea frequently is found at points distant from the intestine. In many cases no real cause of this symptom can be found. It is difficult, for instance, to account for the diarrhea which occurs during a thyroid crisis. Unfortunately, in the minds of many persons, the terms "diarrhea" and "colitis" have been considered synonymous. This is so common that the clinician often finds it difficult to disabuse the patients of the idea that all diarrhea originates in the colon. The diabetic who has diarrhea feels certain that his diarrhea indicates a disease of the intestine. Eventually, this type of diarrhea may be proved to be an entirely independent entity which has no relation to diabetes or to the mechanism responsible for it.

Steatorrhea is a form of diarrhea in which the loose stools contain an abundance of fat. There also are numerous causes of steatorrhea. The two which are probably most commonly encountered are pancreatic insufficiency and sprue. It is more than likely that the mechanism of production of the steatorrhea in these two conditions is different. In sprue, pancreatic enzymes are present in the duodenal contents and the steatorrhea probably results from a failure of proper absorption of fat by a damaged small intestine. In the steatorrhea of pancreatic insufficiency, pancreatic enzymes cannot be demonstrated in the intestinal contents of the duodenum. The steatorrhea in this case probably results from improper splitting of fats taken in.

In cases in which the diarrhea of pancreatic insufficiency is associated with steatorrhea, the stools are bulky, have an offensive odor, and contain excessive amounts of fat. Diabetes, if present, is mild most of the time, except during episodes of acute inflammatory changes in the pancreas, which may be characterized by severe abdominal pain and occasionally by chills and fever in cases in which the condition is severe. Roentgenographic evidence of diffuse calcareous changes in the pancreas may be present.

The treatment of steatorrhea which is the result of pancreatic insufficiency has been most unsatisfactory in the past. Symptomatic measures and the administration of commercial pancreatic preparations have either failed to produce relief or at best have produced only transient relief. Then, too, the diabetes usually becomes difficult to control because of the necessity for dietary changes and the difficulty in estimating the optimal dose of insulin.

In these cases one obviously would search for trouble in the pancreas. In the cases of steatorrhea, there is evidence of a disturbance of the external secretions of the pancreas. It has been suggested that in some of the diarrheas associated with diabetes, there may be a relative decrease in the flow of pancreatic juice and therefore an intestinal disturbance without steatorrhea. A careful analysis, however, of the two types of diarrhea impressed us with the fact that in cases of severe diabetes associated with watery diarrhea, pancreatic enzymes exist in the duodenal contents whereas in cases of steatorrhea, the enzymes might be absent.

It is a well known fact that in diabetes produced in animals by complete pancreatectomy, difficulty in their management has been encountered because of the occurrence of diarrhea. It also has been found that this diarrhea may be fairly well controlled by the addition of bone ash and raw pancreas to the diet. As soon as diets which do not contain pancreas are administered, diarrhea again becomes a serious complication. Various preparations made from pancreatic tissue have not proved satisfactory substitutes for raw pancreas nor has the feeding of pancreatic juice been of great benefit in these animals. On the other hand, the addition of precipitates containing some of the active enzymes of pancreatic juice has given better results. These facts suggested to us that the administration of pancreatic juice or its active substances would be worth a trial in the treatment of the diarrhea of pancreatic insufficiency which affects human beings.

Because of the enzymatic nature of the active substances of pancreatic juice, small quantities may act on a relatively large quantity of food in the intestine and may produce nearly complete digestion. The effectiveness of small amounts of pancreatic juice was demonstrated in the case of animals whose pancreatic ducts were almost completely occluded. Patency of one small duct prevented the development of all the signs of pancreatic insufficiency which are characteristic of complete pancreatic occlusion. The effectiveness of

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small amounts of pancreatic juice was likewise shown by Elman and McCaughan in studies on animals which had pancreatic fistulas from which all secretions were drained. Such animals secreted great quantities of pancreatic juice, and symptoms and changes in the chemical composition of the blood which were similar to those found in cases of obstruction of the upper part of the intestine developed. Death occurred within the first week unless large amounts of physiologic saline solution were administered, but the administration of a few cubic centimeters of pancreatic juice greatly reduced the secretion of pancreatic juice and the subsequent occurrence of symptoms, and prolonged life more or less indefinitely.

METHOD OF PREPARATION AND ADMINISTRATION OF PANCREATIC JUICE

Pancreatic juice for administration to patients was prepared in the following manner: With an aseptic surgical technic, a cannula was tied in the major pancreatic duct and the minor pancreatic duct was ligated while the dogs were under ether anesthesia. A sterile rubber tube was passed through the skin to connect the cannula in the pancreatic duct to a sterile rubber bag placed in a small basket on the animal's side. The pancreatic juice then was removed from the bag once or twice daily. The animals maintained themselves well if a small amount of pancreatic juice was administered by mouth.

Administration of whole pancreatic juice by means of a duodenal tube proved efficacious in the treatment of patients with this type of diarrhea. Because of the inconveniences of this method and the bulk of whole pancreatic juice, we then tried administration of dried precipitates which represented less than 0.5 per cent of the whole pancreatic juice. The following types of precipitates have been found to be active: (1) material precipitated from pancreatic juice by the addition of five volumes of alcohol at a temperature of — 20° C.; this precipitate was dried with cold alcohol and ether; (2) material precipitated by the addition of picric acid; this precipitate was dried and the picric acid was removed with alcohol and ether, and (3) material precipitated by the addition of a 5 per cent solution of trichloracetic acid; this precipitate was dried and the trichloracetic acid was removed with alcohol, acetone and ether. At present, we are using the last preparation.

RESULTS OF TREATING STEATORRHEA WITH PANCREATIC JUICE

The following cases exemplify the results of substitution therapy in the treatment of steatorrhea which is the result of pancreatic insufficiency:

Case 1. An unmarried man, aged thirty-six years, came to the clinic March 9, 1935. For eight years he had had periodic attacks of pain in the upper part of the abdomen, which had been associated with chills, fever and sweats. Between attacks there had been constant soreness in the upper part of the abdomen. The attacks had lasted about four days, and had been initiated by anorexia and abdominal discomfort. The pain had been situated in the epigastrium and had extended to the right and left side and at times to the back, between the shoulders. It had been severe and hypodermic injections of morphine frequently had been required for relief. With the coming of an attack, the patient had felt restless and irritable. During the attack the abdomen had become tight and distended, but had not been sore to touch. Relief had been obtained by crouching or bending forward, or by sitting in a tub of hot water. Vomiting had occurred occasionally, but had produced relief. The chills and fever had continued for several days after the pain had gone. No food had been taken during the attack.

A year before the patient came to the clinic these attacks gradually had subsided, but they had recurred six weeks prior to his admission. An exploratory laparotomy had been performed a year after the onset of the attacks. The preoperative diagnosis had been peptic ulcer, but none had been found. The abdominal organs had been normal, except the pancreas, which had been inflamed. The attacks had continued to occur about eight to ten times each year after the operation. The patient had gone to a hospital for four or five days during most of the attacks. Six weeks before he came to the clinic diabetes had been discovered following one of the attacks of pain. A diet had been instituted and for a time 40 units of insulin had been given daily. The patient had noticed for a long time that his stools had appeared greasy and foamy and had floated on water; they had contained much undigested food but no blood. The diarrhea had been severe until six weeks before his admission to the clinic, when some improvement had occurred.

When the patient arrived at the clinic he seemed ill enough to be hospitalized at once. The value for the blood pressure, measured in millimeters of mercury, was 130 for the systolic and 80 for the diastolic, and his weight was 121½ pounds (55 kg.). The value for the hemoglobin was 13.3 gm. per 100 c.c. of blood; the erythrocytes numbered 4,100,000 and the leukocytes 7,900 per cubic millimeter of blood respectively. The differential blood count was approximately normal. The value for blood sugar was 163 mg. per 100 c.c. A serologic test for syphilis was negative. The urine contained a trace of a reducing substance. Subsequent urinalyses revealed from 1 to 2.4 per cent of sugar. The results of tests of liver function were normal and there was no retention of dye. The value for the bilirubin was 1 mg., that for the calcium was 9 mg., that for the phosphate was 4 mg. and that for the protein was 6.4 mg. per 100 c.c. of serum respectively. Roentgenologic studies revealed a normally functioning gall bladder and extensive pancreatic lithiasis. As a result of a strict diabetic program the urine became free of sugar but the distress in the upper part of the abdomen continued.

After a medical regimen had been employed for two weeks, an exploratory operation was performed (March 22, 1936). An operative diagnosis of chronic pancreatitis with calcification was made by the surgeon, who described the pancreas as being about three times the normal size and diffusely indurated throughout. The common bile duct was dilated to about twice its normal size. Choledochostomy and cholecystostomy were performed. No stones were demonstrated in the gall bladder or its ducts. The postoperative convalescence was satisfactory although somewhat prolonged. The expected improvement, however, did not result and the patient returned to the clinic July 15, complaining of nausea, vomiting and a heavy feeling in the right upper quadrant of his abdomen, but he thought the pains had decreased somewhat in severity. His urine had remained free of sugar. His bowels moved every two or three hours throughout the day and night, the stools being light brown, soft to liquid, frothy, bulky and fatty; they had an offensive odor.

The patient was then given the prepared pancreatic juice through a tube which was passed very cautiously into the duodenum. We began by giving 1 c.c. every hour; the maximal amount given at one time was 2 c.c. In twenty-four hours the number of stools had been reduced from twelve or fifteen to four, and this status was maintained by continued administration of a measured amount of pancreatic juice. In a few days, the stools became

nearly normal. The patient was then dismissed from the clinic and instructed to take minute capsules containing the concentrated pancreatic juice. The patient continued to improve so long as he took these capsules; if he stopped taking them the trouble recurred. It was ultimately found that a minimal quantity of the dried juice was necessary to maintain normal intestinal function.

Case 2. A man, aged sixty-five years, came to the clinic December 4, 1935, because of progressive loss of weight and diarrhea. Five years previously he had weighed 150 pounds (68 kg.). When he came to the clinic he weighed 100 pounds (45.4 kg.). He said that he formerly had been very energetic and had taken a good deal of physical exercise, but that he had gradually become weak, tired and had lacked energy. His stools had been soft or liquid and had contained a great deal of oil and fat. At the time of his admission he was having four to six large, oily stools every twenty-four hours. Sugar first had been found in his urine in 1931. At that time the value for the blood sugar had been 170 mg. per 100 c.c. He had been given an adequate diet and his urine had been free of sugar, but in spite of this he had gradually lost weight.

Examination at the clinic revealed that the diabetes was mild. The value for the blood sugar while the patient was fasting was only 101 mg. per 100 c.c., and the urine was free of sugar. He was constantly hungry and always ready to eat. He commented repeatedly on the fact that the fat he took was not digested. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. The patient appeared exhausted and emaciated. Numerous stools were examined and all contained oil or fat in excess. Their gross appearance was that of an oily fatty mass. Meat fibers were present. Results of examination of a typical stool revealed 21.2 per cent of total fat, 13.8 per cent of which was fatty acid and 7.4 per cent of which was neutral fat. The value for cholesterol was 139, that for the cholesterol esters was 82, that for the total fat was 421, and that for fatty acids was 282 mg. per 100 c.c. of plasma respectively. The value for the serum protein was 5.4 mg. per 100 c.c. The duodenal contents did not contain amylase and trypsin. Proctoscopic examination revealed a normal rectal lining. Roentgenologic studies of the stomach, colon and small intestine did not disclose any intrinsic organic disease. The gall bladder was reported as normally functioning, but there were multiple stones in the pancreas.

We started treatment of this patient by giving a capsule containing the pancreatic extract every four hours. Improvement started on the second day, and by the fourth day, his stools had become nearly normal. We have been able to maintain the normal stools by administering two capsules daily, each of which contains a fifth of the amount of pancreatic extract given at one dose when treatment was started. The diabetes has been readily controlled.

You will recall that this patient was under our observation in December, 1935. For many months, capsules of the pancreatic juice were supplied him. Because of the difficulties of maintaining the supply, he was advised from time to time to try commercially prepared pancreatic enzymes. He has tried every available product. In March, 1937, he wrote that none of them had helped appreciably. After each trial of a new one and its failure, prompt and complete relief followed the use of the one capsule, as described, twice a day. Less than this would not produce striking or lasting results.

COMMENT

It should be emphasized that the results obtained have been gratifying only in the type of diarrhea associated with steatorrhea. One would expect the best results in cases in which there is marked interference or total inhibition of the external secretions of the pancreas. Such a condition exists when obstruction of the pancreatic ducts, as by a stone, occurs.

Fortunately, the association of diarrhea and diabetes is infrequent. With the exception of some of the serious organic causes of diarrhea, it represents one of the most distressing conditions confronting the present day practitioner. The diet advisable for the diabetic is so obviously not the kind one would offer an individual who has diarrhea. Hence, the dietetic problem becomes a real one. Furthermore, the problem of the evaluation of the amount of insulin necessary for control of the diabetes is intensified. Loss of weight may be great and its control is exceedingly difficult.

These experiments bid fair to offer help to at least one type of patient who suffers from steatorrhea. Intensive dietary studies on animals whose pancreatic ducts have been evulsed are under way and we hope these may offer further leads which will point to the control of other phases of this difficult problem.

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DISCUSSION

DR. J. PAUL QUIGLEY (Cleveland, Ohio): Dr. Bargen has called our attention to the fact that diarrhea may occur from some disturbance in the gastro-intestinal tract located higher than the colon. I want to go a step further. Dr. Einsel and I prepared a series of dogs from which the body and fundus of the stomach had been removed and the esophagus anastomosed to the pyloric antrum. The only striking appearance in these animals was the condition emphasized by Dr. Bargen, diarrhea and excessive fecal fat. Practically all the fat in the diet of the animals passed on through.

We haven't developed a complete explanation for this condition. The portion of the gastro-intestinal tract which produces the essential factors of gastric juice has been removed. However, the diarrhea and steatorrhea are not essentially the result of absence of hydrochloric acid and pepsin but are related to the deficient reservoir function of the stomach and the consequent excessively rapid propulsion of food through the intestine.

Our results emphasize the possibility of diarrhea and steatorrhea developing from a disturbance not primarily located in the colon or pancreas.

DR. A. C. IVY (Chicago, Ill.): Dr. Bargen's report implies that pancreatic juice, dried or extracted, is more potent or more favorably administered than pancreatin. I doubt the truth of that implication and, before I believe it, a lot of good experimental evidence will have to be supplied.

I know of nothing at present in pancreatic juice that is not present in properly prepared and potent pancreatin; as a matter of fact, there is something present in pancreatin that is not present in pancreatic juice, which we do know is of value to the organism, namely, lecithin, which contains choline.

Why have a number of physicians been disappointed with the results obtained on the administration of pancreatin to patients with suspected pancreatic achylia? The first reason is that the pancreatin given the patient has not been a potent preparation. At the drug stores in Chicago a year ago, I bought six different preparations of pancreatin. We found only three preparations out of the six worthy of presentation to a patient.

The second reason is that adequate quantities of pancreatin are not administered. Two, three, or four tablets

after a meal are usually given. In our animals in which we have been studying oral enzyme therapy, we have given 25 grams of pancreatin a day in the form of powder or enteric coated tablets, and we have shown that the enteric coating increases the effectiveness of the orally administered pancreatin.

When we give pancreatin to our patients, we must know that it is potent. We can't rely on the Council of Pharmacy and Chemistry for such potency, because they do not accept pancreatin or any other enzyme for oral administration, and the U.S.P. requirements in regard to pancreatin are not to be praised; so, if we are going to give pancreatin, we should know first, by having a competent chemist test it, that it is potent, and, when we give it, we must give it in adequate quantities.

We have two patients with pancreatic achylia and we have demonstrated that 25 grams of pancreatin, or 75 five-grain tablets, given per day, with and after meals, is effective. I say that on the basis of reliable evidence, and not on the basis of the patient's feelings or reports.

I was glad to see that Dr. Bargen showed the absence of enzymes from the duodenal drainage in his patients, but he did not say he had analyzed the stools chemically for fats, protein, and starch.

I think the only reason why the Council of Pharmacy and Chemistry of the American Medical Association does not accept pancreatin for oral administration is that there is very little good evidence in the literature showing that pancreatin is effective in man. There is plenty for the dog, which now demonstrates that it is effective. In many of the reports in which pancreatin has been used in man, analysis of duodenal drainage has not been done, to prove that a case of pancreatic insufficiency is actually being treated; and, secondly, the stools have not been examined chemically under dietary control before and after treatment with pancreatin.

The only way that one can establish scientifically that pancreatin is or is not effective in a particular patient, is to place the patient on a diet, collect the stools and analyze them for fat, nitrogen, and carbohydrate, and then repeat the analysis after pancreatin. When this is done on a sufficient number of patients, then we will have data which will establish, I believe, that oral enzyme therapy is effective in human subject suffering pancreatic insufficiency.

DR. WILLIAM C. BOECK (Los Angeles, Calif.): I have enjoyed hearing Dr. Bargen's paper which has brought the subject of steatorrhea before us again. I trust that the new method of treatment will be available to the rest of us who have such patients under our care.

I have the excuse of appearing before you simply to recount the history and treatment of another case in which steatorrhea was the prominent finding but which apparently was due to extrinsic factors outside of the organs of the gastro-intestinal system.

This case was that of a physician, 45 years of age whose illness lasted for one year. He had a persistent diarrhea which proved to be a steatorrhea, for the stools were made up mostly of fatty acid crystals. They were as plentiful as to appear like the sediment of a turbid specimen of urine.

He had abdominal distention and marked tenderness in the left upper hypochondrium. There was adenopathy of the axillary and inguinal glands. He had lost some twenty-five pounds in weight.

Physical examination and X-rays were negative for tuberculosis. Achlorhydria was present. The small intestine showed "laking" of barium in the jejunum and upper ileum suggestive of that described in cases of sprue. The blood picture was that of a moderate secondary anemia, with erthryocytes varying from 3,500,000 to 4,000,000, and hemoglobin from 75 to 85 per cent (Sahli) most of the time; a persistent leucopenia of 2,500 to 3,500 leucocytes was present all the time until one month before his death when it became normal.

Biopsy of an inguinal gland revealed a picture somewhat resembling tuberculosis, but no pathologist would agree that it was. Later, laparotomy was performed. The mesenteric glands were all enlarged, especially in the area of the jejunum and pancreas, but not in the region of the terminal ileum. A large mass of mesenteric glands was found at the origin of the mesentery near the pancreas. The small intestine and colon appeared to be normal.

The biopsy examination of one of the mesenteric glands showed almost complete disappearance of all lymphoid tissue with replacement by fat present in reticulocyte cells and deposits of cholesterol crystals. The microscopic preparations of this tissue were examined by several prominent pathologists throughout the country but no one made a definite diagnosis. It was thought that the condition was some form of lymphoma.

As to treatment, liver extract was used extensively, along with dilute hydrochloric acid, a fat-free diet, then later a normal diet, but no benefit occurred until the patient was given X-ray treatment. Then the diarrhea ceased almost entirely and also the steatorrhea. The adenopathy and abdominal distention disappeared. The patient gained 7 pounds in the next four months, but weakness persisted. One month before he died, his white cell count became normal and we were hopeful that his change portended a better prognosis. However one month later he suffered from acute cardiac decompensation and died a few days later.

Autopsy findings were those of cardiac dilatation. The pancreas, liver, adrenals, and mesenteric glands all appeared to be normal. There was no evidence of fat and cholesterol deposits in the glands, but some occurred in the walls of the small intestine with some mucosal atrophy.

Whether or not his case belongs in the category of those described as acute or chronic mesenteric adenitis or as some form of lymphoma I do not know but it illustrates the occurrence of steatorrhea from some disturbance extrinsic of the gastro-intestinal system, which vanished after X-ray treatment but the treatment did not cure the patient.

DR. J. ARNOLD BARGEN (Rochester, Minn.) (closing the discussion): I appreciate the discussion of Drs. Boeck, Ivy and Aaron. I tried to bring to your attention only one other method of aiding some of these very miserable people.

I believe, after hearing Drs. Aaron and Ivy, that in the past we have at times not used enough pancreatic extract. This very simple method came through Dr. Bollmann's work on animals and we were able to control the diarrhea of man. We were able to control it in one case by administering two small capsules of the powder daily. The patient had tried all kinds of drugs on the market, including very large amounts of pancreatic extract. Whole pancreas has been used sporadically but not enough to permit us to conclude how it would compare with this pancreatic juice. However the second patient received 75 to 100 grains daily of pancreatic extract of a preparation supposedly potent without effect, whereas two small capsules of the dried juice controlled his symptoms.
how it would compare with this pancreatic juice.

The pancreatic juice is not a cure-all. Some patients have not received adequate relief. A minister from the South received what we thought was an adequate quantity of these capsules but he was not particularly helped. All persons who have these types of diarrheas are thoroughly miserable and a certain number of them, I think most of them, will be helped when the pancreatic ducts have been occluded. Whether there are enough of them even to

warrant making such a preparation commercially, I do not know. In reply to Doctor Ivy's question about stool analysis, I should like to say that in all these individuals careful chemical analysis was made in all, as indicated in the second case.

Regarding the different causes of steatorrhea, Dr. Boeck mentioned an entirely different type. I think we must keep in mind that there is a steatorrhea which is probably due to a failure of the proper splitting of fats, and a steatorrhea which probably is due to failure of absorption. The latter may be associated with sprue. I saw a patient who had a definite clinical picture of sprue and tuberculosis of the abdominal lymph nodes. At necropsy there was marked atrophy of the intestinal mucous membrane. That patient presented a picture such as Dr. Boeck has described, but the course of the disease was not affected in the slightest by these capsules.

I hope this study may result in a stimulation to further study of this type of diarrhea and a trial of an adequate quantity and an adequate type of pancreatic product.

The Diagnosis and Treatment of Acute Non-Hemorrhagic Pancreatitis*

By

ROBERT ELMAN, M.D.
ST. LOUIS, MISSOURI

THE current conception of acute pancreatic disease is usually confined to the lesion often called pancreatic necrosis or acute hemorrhagic pancreatitis. The pathology of this remarkable condition is well known, its course is nearly always progressively downward and is associated with a high mortality even when an emergency operation is carried out. Acute pancreatic necrosis is, however, a relatively rare disease and in recent years has not evoked much interest in spite of the mystery which still surrounds its pathogenesis.

Acute pancreatitis which is not associated with necrosis, i.e., nonhemorrhagic pancreatitis, has from time to time been discussed in the literature as a mild type of pancreatitis which stopped short of actual destruction of the gland and subsided. In general, this group of patients comprises those operated upon with a diagnosis of pancreatic necrosis (or some other acute abdominal condition) but in whom at laparotomy the pancreas presented no hemorrhage or necrosis, but merely an edema or induration particularly of the head of the gland (1, 2). The possibility, however, that the pancreas is very often the site of acute inflammation which subsided has never been very widely held, in spite of the fact that surgeons, during the course of cholecystectomy, have frequently found the pancreas to be indurated and enlarged. This association of pancreatic with cholecystic disease has, of course, been repeatedly observed and may account for the fact that the lesion in the pancreas has consistently been afforded little consideration in favor of the more well known lesions in the gall bladder and liver. It has been my experience that this type of pancreatitis is relatively frequent but that it nearly always masquerades as another lesion; because of these considerations I have made a clinical study of a number of these cases. Review of the literature has been made in previous papers (1, 2, 3).

The present observations concern patients who suffered acute subsiding attacks of epigastric pain due undoubtedly to an acute process in the pancreas, most likely an inflammation, in most cases at least, but not of the hemorrhagic type and without evidence of necrosis. In most of these patients the original diagnosis did not refer to the pancreas; many were suspected of suffering from biliary colic, others of acute cholecystitis, perforated peptic ulcer, acute appendicitis, acute intestinal obstruction, and a few, coronary thrombosis. In the first cases observed the true diagnosis was revealed only at operation when the lesion in the pancreas was noted. Later it was possible to make a clinical diagnosis by studying the blood for its concentration of amylase. This determination when made at the height of the patient's symptoms and repeated as the clinical manifestations subsided, revealed a striking correlation with the course of the attack. In a few patients both objective evidences of pancreatitis were obtained, i.e., the rise and fall of the blood amylase and anatomical changes through biopsy of the pancreatic lesion.

As far as the clinical behavior itself is concerned the bed-side manifestations frequently gave only suggestive indications of the true nature of the disease. In all cases, the attacks were severe and disabling, the patient seeking bed rest at once. The pain was often cramp-like in character and nearly always accompanied by vomiting. While located in the mid epigastrium, the pain was often more severe to the right or to the left of the midline and occasionally was diffuse. A nearly constant feature was the reference of the pain to the small of the back, i.e., over the spines of the lumbar vertebrae. Occasionally the pain was referred to the mid-scapular region. Attacks varied in severity and duration, but rarely did they exceed four days before subsidence. Only occasionally were patients seen in their first attack; a history was fre-

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quently obtained of a few to many previous attacks, sometimes extending back for many years.

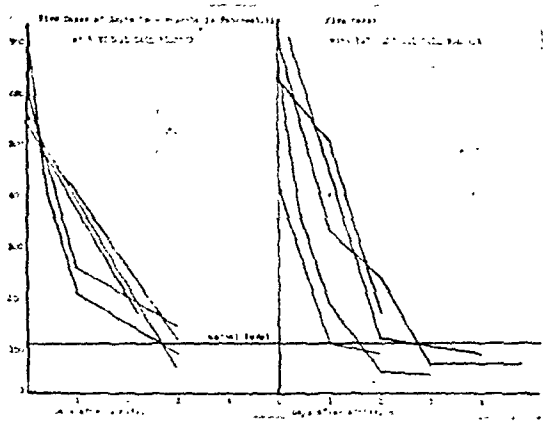
On examination, these patients, when seen at the onset of the attack, were in obvious distress due to severe pain; though prostrated they were not in shock as shown by a normal pulse and blood pressure; there was no cyanosis or evidence of circulatory collapse. The temperature, however, in a few cases became moderately elevated. The abdomen was often slightly distended and diffusely tender but nearly always revealed on careful palpation a transverse zone of more marked deep tenderness in the epigastrium over the region of the pancreas. In a few cases I was also able to outline a Head-zone of skin hyperesthesia along the left costal margin. In nearly all patients a mild scleral icterus could be made out especially if the examination occurred during daylight; others showed more evident jaundice. Aside from the blood amylase findings to be described in detail below, the laboratory tests were non-specific. A leucocytosis was frequently observed but often absent; routine urine examination was negative. However, a high icteric index was noted when looked for and in many cases urobilin was found in the urine. Although I feel that the above outlined clinical picture may perhaps enable a reasonably accurate impression to be made, I have refused to make a definite diagnosis of acute pancreatic disease unless a high blood amylase was found in a specimen obtained while the patient was suffering from acute symptoms; with subsidence of the attack the concentration of the ferment progressively decreased. In all the cases herein reported such determinations were made.

The basis for the use of the blood amylase in the diagnosis of pancreatic disease rests on many experimental observations, which show, in general, that obstruction of the pancreatic duct and inflammation of or injury to the pancreas is associated with a marked elevation in the normal level of the amylase in the blood. This correlation has been so uniformly confirmed that it really does not matter whether the amylase in the blood is wholly or merely in part of pancreatic origin. For diagnostic purposes it suffices that the blood amylase reflects, very rapidly and markedly, acute changes in the pancreas. I had occasion to note this fact many years ago while working with dogs, in whom a complete external pancreatic fistula had been installed. The tube draining all of the secretion was clamped, producing a sudden total obstruction. Within 15 minutes the blood amylase had doubled in value; in an hour it had quadrupled. After 24 hours of total pancreatic obstruction the blood amylase was 20 times above its normal level. It has also been shown (Somogyi) that mere palpation of the pancreas during a laparotomy is associated with a transient but marked increase in the level of blood amylase.

SUMMARY OF CASES

(All showed characteristic blood amylase curves, shown in accompanying charts)

	Case age, sex)	Duration of attack (days)	Previous Attacks	Admission Diagnosis	Jaundice	White Blood Count	Highest Temp. (F)	Cholecystogram	Remarks
Chart 1a	39 F	10	many	Biliary Colic	+	9,200	99°	normal	—
	19 F	4	several	Hysteria	+	11,000	100°	normal	Well 1 yr. later
	56 M	4	yes	Intestinal Obst.	+	30,000	102°	normal	Well 6 mo. later
	42 F	6	yes	Perforated Ulcer	+	13,000	100°	normal	—
	37 M	3	yes	Intestinal Obst.	?	15,000	103°	normal	Well 2 yrs. later
Chart 1b	38 M	2	yes	Biliary Colic	+	8,000	98°	No shadow	Cholecystectomy; no stones, pancreas hard
	67 M	3	yes	Biliary Colic	+	24,000	101°	No shadow	Refused operation
	29 F	3	yes	Biliary Colic	+	12,000	100°	Faint shadow	Refused operation
	35 F	3	yes	Biliary Colic	+	18,000	101°	No shadow	Cholecystectomy; stones pancreatitis
	27 F	3	three	Biliary Colic	+	20,000	101°	No shadow	Cholecystectomy; no stones
Chart 2b	58 M	3	three	Biliary Colic	+	11,000	101°	?	—
	73 F	2	?	Dementia	?	18,000	102°	?	Complete recovery
	68 M	3	many	Ac. Cholecystitis	+	14,000	102°	?	—
	66 F	1	no	Coronary Occlu.	+	20,000	98°	?	—
	64 M	5	one	Biliary Colic	+	6,000	99°	?	—
Chart 2a	32 F	3	yes	Pancreatitis	+	12,000	101°	—	Previous cholecystectomy
	42 F	1	yes	Coronary Dis.	0	—	—	—	Previous cholecystectomy
	54 F	2	yes	Intestinal Obst.	0	—	—	—	Previous cholecystectomy



Blood Amylase (as mg. of glucose per 100 c.c. blood)

Chart 1a (see page 87) Chart 1b

In all of the patients herein reported a marked elevation of the blood amylase was found at the first examination. The highest values were noted in those examined early in the course of their attack and in those with the severest attacks. In all, however, a progressive fall in the blood amylase was observed, often within a matter of hours, more commonly after a day or two, but in most instances in striking correlation with the subsidence of the patient's symptoms. Whenever the serum was examined for bilirubinemia it was found in moderate degree, which, however, with the amylase, returned to normal.

TREATMENT

The therapy advised and carried out in these patients (after the attack had subsided) depended upon the presence or absence of associated cholecystic disease as revealed by clinical and laboratory study, especially by cholecystography. They may be divided into three groups, those with, those without cholecystitis, and those who had already been cholecystectomized.

1. If stones were demonstrable or if an abnormal shadow or no shadow followed the intravenous test operation was usually advised. I say usually because in a few instances the cholecystogram became normal with the lapse of time. When operation was carried out soon after an attack the existence of a diseased pancreas was detected, provided that the gland was exposed adequately. Visualization of the pancreas (by separation of the gastrocolic omentum) frequently revealed fat necrosis, and biopsy of the indurated tissue showed interstitial inflammation, edema and fibrosis. The diseased gall bladder was removed and the common duct explored through the cystic duct; in each instance I have observed an impediment to the passage of a bulb-tipped probe into the duodenum. This I interpreted as a spasm of the sphincter of Oddi which was dilated with bulbs of increasing caliber. A cysticocholedochostomy, i.e., drainage of bile through the cystic duct was then carried out.

2. When cholecystography revealed a normal shadow without stones, a medical regime consisting essentially of a liberal diet taken, however, in small frequent feedings was instituted; a mild sedative such as phenobarbital was also prescribed, because I felt that the fear of these attacks in many patients may have played a role in initiating some of them. These patients eventually got well; the attacks subsided in frequency and thus far many of them have required no further therapy. The follow-up has, however, been too recent to draw any definite conclusions.

3. When the patient has already had a cholecystectomy the same medical regime was followed. One must, to be sure, exclude the existence of stone in the common duct in this group of patients; this differentiation can usually be made on clinical grounds alone. If a stone is present a secondary operation is obviously indicated. It has been my observation, however, that in most instances operated upon for such a reason, no stone was found in the common duct but that the pancreas showed evidence of inflammatory disease.

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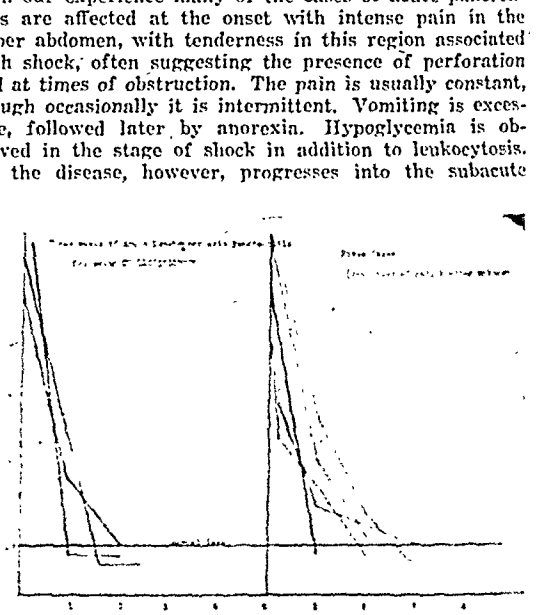
DISCUSSION

DR. JULIUS FRIEDENWALD (Baltimore, Md.): Dr. Elman has presented a highly interesting and important paper. It is a well accepted fact that certain instances of acute pancreatitis are occasionally observed which, although ushered in with fulminating symptoms, soon lose their intensity and continue as milder types of the disease. Among such cases, without doubt, may be included some referred to by Dr. Elman.

There are, however, other cases which are extremely stormy in their onset, in which operation is contemplated, but delayed due to shock or other complications which also occasionally recover even without surgical intervention.

Up to recently most of the milder instances of this affection have been incorrectly diagnosed or have been recognized only at operation. It is to these milder forms that Dr. Elman has called special attention in his presentation, and in which the diagnosis was confirmed by means of the determination of the amylase concentration in the blood.

In our experience many of the cases of acute pancreatitis are affected at the onset with intense pain in the upper abdomen, with tenderness in this region associated with shock, often suggesting the presence of perforation and at times of obstruction. The pain is usually constant, though occasionally it is intermittent. Vomiting is excessive, followed later by anorexia. Hypoglycemia is observed in the stage of shock in addition to leukocytosis. As the disease, however, progresses into the subacute



Blood Amylase (as mg. of glucose per 100 c.c. blood)

Chart 2a (see page 87) Chart 2b

stage, or in the milder types, hyperglycemia may be encountered. In this form, subsidence of symptoms with recurrences is not infrequently noted, and the symptoms appear as mild manifestations of anorexia, weakness, upper abdominal distress, and pain often to the left of the mid-epigastrium and back, with constipation or diarrhea associated with fatty stools. Tenderness over the entire epigastrium is noted.

Many of these cases are complicated with cholelithiasis and present a history of previous attacks of gall stone colic. All of our operated cases, as well as a few in which surgery was not undertaken, presented this complication.

In the milder instances of this disease, conservative management is advisable at least for a certain period of time, especially in the absence of gall stones instead of undertaking a surgical procedure at an inopportune time. In many of these cases, under proper dietetic restrictions, with the addition of occasional duodenal drainages and symptomatic medication, the acute stage lessens in intensity and finally subsides.

Inasmuch as the symptomatology of this affection, especially in the milder types, is by no means characteristic, Dr. Elman has contributed a valuable lesson in the diagnosis by emphasizing the importance of the presence of a high blood amylase content in the acute stages of the disease and its gradual decrease and disappearance with the subsidence of the attack and improvement in the patient's condition. It seems evident, therefore, that if this test be applied more frequently, many hitherto undetected instances of this affection can be recognized at an early stage. Attention should be directed to the fact, as Mahner, as well as others, has pointed out, that a high diastase content likewise occurs in the urine of relatively mild cases of acute pancreatitis, which is also an indication and gives further proof of organic disease of the pancreas.

Another test, the serum lipase reaction, is similarly of diagnostic value especially in the acute or subacute cases, and may likewise be taken advantage of in the diagnosis of obscure cases.

DR. M. A. McIVER (Cooperstown, N. Y.): I was very much interested in Dr. Elman's paper and the very interesting group of cases he described. I don't doubt for a moment, in fact I think it is universally recognized, that there is a group of cases of mild acute pancreatitis that really constitutes a clinical entity; but I think it is often very difficult to be sure of the diagnosis, and I take it that in a great many instances it would really come down to dependence on the amylase test.

I should like very much to ask what Dr. Elman's experience has been with this test in cases of frank hemorrhagic pancreatitis. I have been rather disappointed in it as a diagnostic test in the few cases of the hemorrhagic type in which we have tried it.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): Von Bergman and his associates have reported this type of condition for the last several years and have made valuable contributions to the diagnosis of the disease. They classified it as a subacute pancreatitis and I am wondering whether the entity described by the essayist is not identical. One should always be cognizant of the possibility of this condition. Aside from metastatic infections, there are four commonly accepted etiological factors giving rise to subacute and acute forms of pancreatitis, namely, cholecystic disease, obesity, perforated ulcer of the stomach and duodenum implicating the pancreas and syphilis. The last case of this type which I saw, that was convincing from a purely clinical standpoint, was about a year and a half ago in a middle aged obese male. For five months prior to his admission he had been treated on the basis of a high, perforating ulcer of the stomach, the presence of which we were unable to confirm. Other diagnoses were left renal stone, spondylitis, gall bladder disease with transposition of symptoms, etc. We had the good fortune to see him in one of his subacute seizures, at which time he had the characteristic radiation from the upper left epigastrium through to the back, hyperasthesia, marked tenderness, elevation of serum lipase and urinary diastase, etc. Cholecystographic examination was negative.

On dietary restrictions, with marked reduction in fat and protein, and increased carbohydrate, he made a prompt recovery and has not been troubled since.

DR. HENRY A. RAFSKY (New York, N. Y.): Dr. Elman has presented a distinct clinical entity. These cases are very often difficult diagnostic and therapeutic problems. This was graphically illustrated in a patient who was admitted to the Gastro-Intestinal service at the Beth Israel Hospital. The case presented the clinical picture of intestinal obstruction. The surgical division refused to operate upon this patient because it was thought that he would not survive. Medical treatment was then tried. I shall discuss the treatment shortly, but first I would like to point out some interesting phenomena which were noted. The patient ran a febrile course for several days with daily fluctuations of his temperature. When fever was present a hyperglycemia and glycosuria were observed. When the temperature fell, the blood sugar and urine were normal. The treatment consisted in decompressing the stomach and duodenum by duodenal instillations. His symptoms subsided. It was thought of interest to stop the treatment to see what would happen. The symptoms recurred. Then duodenal instillations were again instituted and the patient made an uneventful recovery. He has not had a recurrence of the symptoms. An X-ray of the gall bladder showed it to be enlarged; no stones were found.

DR. JOHN R. TWISS (New York, N. Y.): I should like to ask Dr. Elman, in regard to the treatment of these conditions, whether he does not feel there is a certain element of danger in doing a cholecystectomy. In our experience this type of pancreatitis is likely to be recurrent. The common bile duct goes through the pancreas and, in the absence of the gall bladder, a serious problem is likely to be presented at a future date. For that reason, in the New York Post Graduate Hospital, we have preferred to do a cholecystostomy rather than a cholecystectomy.

DR. ROBERT ELMAN (St. Louis, Mo.). (closing the discussion): I wish to thank the discussers for the many interesting points brought up in regard to the paper.

As to Dr. McIver's question, the blood amylase is also elevated in acute pancreatic necrosis; the curve is perhaps more prolonged in the beginning, but drops very rapidly after a few days. This drop, however, is not due to subsidence of the inflammation, as revealed by the cases that have come to autopsy. Two cases of pancreatic necrosis died without operation which was refused in both instances. At autopsy the entire pancreatic gland had become destroyed, i.e., there was no pancreatic tissue to produce amylase. This brings up the question as to the source of blood amylase; there is much evidence to show that the pancreas is the source of a large amount of it, if not all.

Although the high blood amylase does not reveal the nature of the process in the pancreas, there has been no difficulty in our cases in saying here that this is a patient that has non-hemorrhagic pancreatitis, and that operation isn't necessary; the decision is made on clinical grounds alone, solely because of the circulatory collapse which is so characteristic of pancreatic necrosis and which is absent in non-hemorrhagic pancreatitis.

In regard to Dr. Eusterman's question, many of the reports of subacute and other types of pancreatitis are based upon purely clinical surmises; disease of the pan-

creas is so difficult to diagnose at best that I haven't considered any of the reports in the literature except those in which amylase studies or lipase studies have been made, or in which the organ was observed anatomically at operation or at autopsy; otherwise one has difficulty evaluating many observations which rest upon rather inconclusive evidence in regard to the presence of a lesion in the pancreas.

Dr. Rafsky's question in regard to the temperature is interesting because most of our patients showed at one time or another an increase in temperature, sometimes as high as 102 or 103 degrees F., which usually subsided though sometimes recurrent, in the course of forty-eight hours.

The large gall bladder is also an interesting point. Although I have not made such an observation, many of the cases reported in the literature showed a dilated viscus during operation, when performed during the acute attack; many of them, moreover, contained no stones. An obstruction at the lower end of the common duct, as it traverses the head of the inflamed pancreas, may be a mechanism in the production of the dilated gall bladder as well as of the jaundice.

Dr. Twiss brought up the question of cholecystectomy. I believe that in itself cholecystectomy has a beneficial effect; there is evidence from a number of sources that the common duct and the sphincter of Oddi dilate and the sphincter becomes insufficient following removal of the gall bladder. This is perhaps the explanation of the fact that many of these patients do not have a recurrence of symptoms. However, Dr. Twiss' observation that they may have recurrent pain (I cited above three such patients) indicates that this mechanism does not operate in all instances. I have felt that if spasm of the sphincter of Oddi is the etiological mechanism, dilatation at the time of operation should also be carried out, as well as the cholecystectomy; doubtless further research will indicate the proper procedure.

Back Pain in Lesions of the Gastro-Intestinal Tract, with Particular Reference to Duodenal Ulcer*

By

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BOSTON, MASSACHUSETTS

ALMOST all the ills that flesh is heir to may cause pain in the back. We have come to recognize at a glance, and to pigeon hole back pain of certain types and back pain in association with other symptoms with hardly an error. Nine times out of ten we are right, but occasionally pain in the back will lead us astray and even with all the aids that medical science affords we fail utterly to arrive at the correct diagnosis. It is also true that lesions of the back, particularly lesions of the spinal meninges may cause abdominal discomfort simulating disease of abdominal viscera. Without going over the records I can recall two gall bladders, two appendices, one fibroid and one kidney that had become surgical specimens prior to the removal of the true cause of pain; namely, a tumor of the dorsal cord.

As a neurosurgeon I see a good many cases of intercostal neuralgia, tumor of the spine, and what not and have learned to be wary of pitfalls but errors in diagnosis will creep in. We all recognize the existence of and fear the silent ulcer of the duodenum which strikes murderously, without warning; the first evidence of which is hemorrhage or perforation. We must not forget the frequency with which ulcer will conceal its presence behind a smoke screen of back pain.

Your President, Dr. Chester M. Jones, has been much interested in the production of pain by means of a balloon in the gastro-intestinal tract and his experimental data fits in perfectly with the small group of cases I wish to report. In all seven of these patients the main symptom was pain in the back with little or nothing that would suggest a lesion of the duodenum.

Case one happens to be myself. Many years ago, I began having quite severe pain in my back. This pain usually began in the late afternoon and was particularly noticeable if I had driven my car a good deal during the day. The pain was dull in character, seemed to centre at my 5th or 6th dorsal vertebra and was not associated with any abdominal discomfort. I wore a back brace for nearly a year and did posture exercises with fair regularity. Finally it was noticed that the pain was relieved by taking food. This fact made us suspicious and on X-ray evidence a diagnosis of pyloric spasm and later of ulcer was made. During the years which followed I tried to keep track of my pain, observing its location and its association with other symptoms. I had a good deal of abdominal pain, but many times for no apparent reason the pain would be solely between my shoulder blades, sometimes to the right and sometimes to the left. A most interesting and often repeated experience was a rather sharp tingling pain streaming down the ulnar surface of my left arm. This pain was always associated with a sense of chilliness and usually with such active gastric peristalsis that I could feel it. Another peculiar symptom was excessive salivation associated with pain just to the left of the 5th or 6th dorsal vertebra. It may be of interest to you to know that since resection of the ulcer seven years ago, I have been perfectly well. My ulcer was of the saddle type, involved both the duodenum and pylorus and had evidently leaked a little posteriorly at some time.

Case two was that of a woman of 48, sent to me by Dr. Richard Ohler. She had a history of attacks of pain in the back and left chest running back to 1907. She was said to have had pulmonary tuberculosis but there is no history of any positive evidence of that disease. Four years ago the pain was so severe that she was in bed or on the sofa for four months. The attack for which I saw her had been going on for seven months. The pain was increased by exertion and by driving her car. The pain was in her left back, circled around the 5th or 6th rib and stopped sharply at the midline in front. She stated that the pain would vary in intensity and that the skin in the region involved was tender. There was some pain in the arm at times and deep breathing caused sharp twinges

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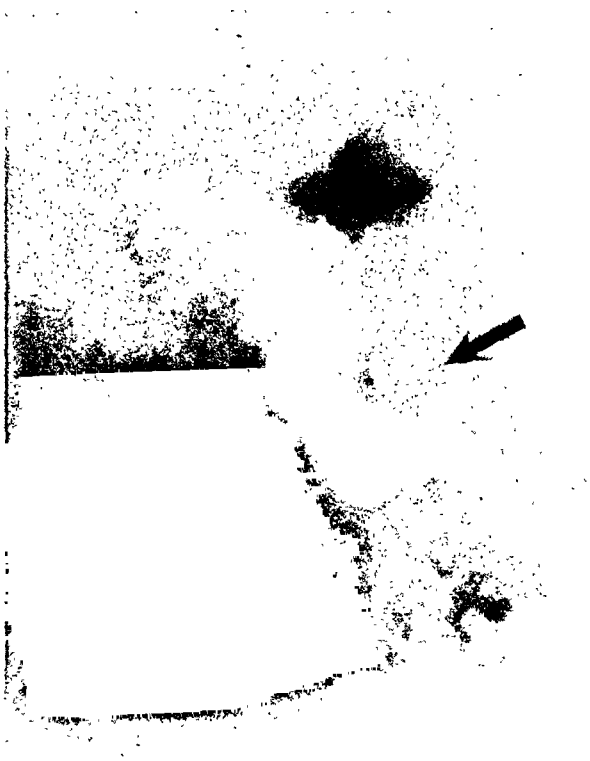


Fig. 1. X-ray Case No. 3. Showing ulcer. (M. G. H. U47867).

of pain in her left chest. She denied indigestion or abdominal distress. Her bowels were constipated. She was taking a good deal of codeine and some morphine to control the pain.

Examination was negative except for definite hyperesthesia girdling the left side of her chest at the level of her pain. She was carefully studied in hospital and all tests including lumbar puncture and electrocardiogram were negative except for an X-ray diagnosis of arthritis of the spine and a white count of 11,000 to 13,000. Gastro-intestinal X-ray examinatioan was not done. A week after she left the hospital she had a massive hemorrhage and after repeated transfusions was operated on by Dr. R. H. Smithwick as an emergency. Exploration revealed a large ulcer of the posterior wall close to the ampulla of Vater with hemorrhage from a vessel in the pancreas. The vessel was tied, pylorus and first portion of the duodenum resected and a posterior gastro-enterostomy performed as it was impossible to resect the ulcer. Her convalescence was stormy but complete and at no time has she had any return of her old pain.

Case three followed within a few weeks. The patient was a physician aged 60 with a history of rheumatic heart disease eighteen years before. As he was recovering from this illness he began having attacks of "neuralgia" starting with a stabbing pain in the back and encircling his chest on both sides to the substernal region. These attacks were brought on by exertion, excitement or fatigue and relieved only by morphine. At times he was unable to sleep on his left side. His history states under gastro-intestinal tract, "Appetite good. Well rounded diet. No acid eructations, tarry stools, gas, constipation, or deep abdominal pain."

He was carefully studied and lumbar puncture done. As his total protein was 77, a lipiodol examination was made which was negative. His spine showed arthritis. X-ray examination of the gastro-intestinal tract showed a small hiatus hernia and duodenal ulcer with a deformed cap.

He was put on a gastric regime and on account of the severity of his pain was given a bilateral paravertebral alcohol injection with marked relief. He did not believe that ulcer played any part in his condition, went back to his regular diet as soon as he left the hospital and nearly died of hemorrhage a few weeks later. Since then he has been on a definite gastric regime and recent X-ray examination shows that his ulcer has healed. He is having no pain in his back.

There is no need to cover in detail the other four cases. Case four had right sided pain extending round to the lower end of his sternum and no gastro-intestinal disturbance. He also had a posterior wall ulcer in the second portion of the duodenum. He was operated on by Dr. R. H. Smithwick, the procedure being similar to that carried out in case two, except that there was no necessity of controlling hemorrhage. He has had no return of his old pain since operation.

Cases five, six and seven were found for me in his own files by Dr. Chester M. Jones. In number 5, the story is very similar to the others, pain coming on after rowing on a college crew late in the afternoon. There is, however, a history of mild indigestion. After a long period of orthopedic treatment which was of no avail, X-ray examination was made of his gastro-intestinal tract. This was done largely for purposes of exclusion. The examination revealed the presence of a frank ulcer.

Cases six and seven are similar except that in both instances there was a history of indigestion. Number six insisted that the back pain could have no connection with the ulcer pain which he had had for years. In both of them the back pain was out of all proportion to the rest of the picture. Both showed typical ulcer. These last two cases are not so startling as the first five, but they are suggestive.

These cases fit in very well with Dr. Jones' experiments with the balloons. Of 24 subjects in which the balloon was in the duodenal cap only one felt pain in the back alone and three had pain that went through from the xiphoid to the back.

Thus in the balloon experiments back pain is rare, as it is in the clinical cases, but it does occur. The level of the back pain coincides with the level in our patients. In the second portion of the duodenum six individuals referred the pain straight through to the back or around the costal margin. You will remember that one of our cases had proven ulcer of the second portion of the duodenum. The level in the balloon experiments would seem to be slightly lower than in our patient.

There are two other factors that may be of interest. One is the posterior position of the ulcer in at least four of our cases and the fact that three and possibly four had eroded through the posterior wall, involving the pancreas in at least two.

The more I theorize on the pain pathways from the duodenum and the reasons for the wide variation of the position of the referred pain the less do I feel we know about this subject. We know that the splanchnic nerves enter the cord from the 5th to the 12th dorsal levels and it would be reasonable to suppose that stomach and duodenum would be represented in the upper part of this portion of the cord.

Also we know that divulsion of the splanchnic nerves under local anesthesia causes severe pain.

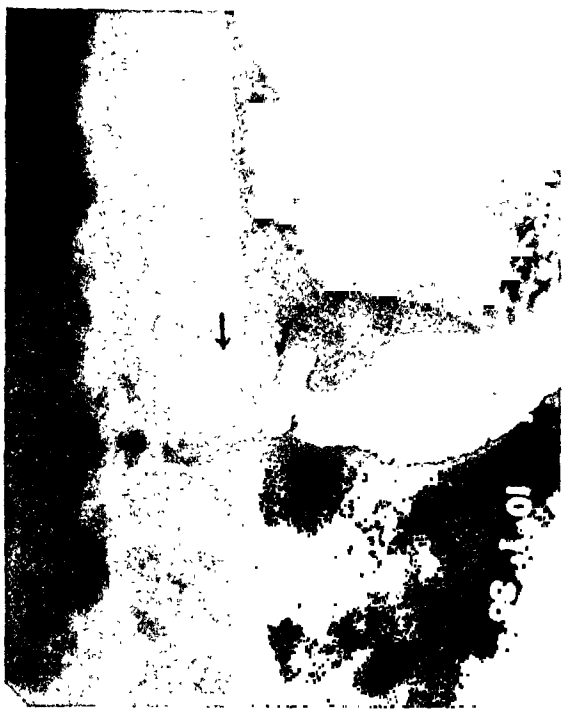


Fig. 2. X-ray Case No. 4. Showing ulcer. (M. G. H.-B. M. 25489).

Unfortunately, the preoperative medication used in operations for splanchnicectomy prevents these patients from giving an accurate description of the pain. But if this pain represents the somatic distribution of splanchnic fibres why should it vary so much? Why should it not always be substernal? And also why should not pain from the back wall of the duodenum be referred to the right side of the body and not the left. It seems that we must fall back on other factors. It would seem probable that the pain is due, in part at least to spasm of the muscle of the gut. If so, the actual position of the ulcer in the circumference of the intestine would not be so important. Perforation with involvement of the pancreas and possibly the posterior portion of the parietal peritoneum may tend to throw the reference of pain through to the back. We must admit our own weakness and hope that further experimental work will clear this matter up.

I have had far less experience with patients in whom back pain has been caused by lesions of other portions of the gastro-intestinal tract. We all know that pain in the low back may be caused by lesions of the rectum and our colleagues in the Genito-Urinary Department are all familiar with the peculiar pains caused by lesions of those systems. It seems to me that these examples, the extraordinary distribution of cardiac pain and our knowledge of gall bladder pain permits us to generalize on referred pain from any part of the intestinal tract. I believe we can expect that a certain small percentage of lesions anywhere in the gastro-intestinal tract will be signalized by pain in the back without the signs we usually associate with gastro-intestinal disease.

Certain it is, that pain in the back or pain radiating about the chest may be the only sign in duodenal ulcer, even in extensive perforating ulcer of the posterior wall of the duodenum. It behooves us, gastro-enterologists, orthopedists, neurosurgeons and general practitioners alike, to remember this fact.

It is by our errors that we learn. The fact that I, and others with me, have erred in diagnosis in this group of patients is my reason for addressing you. I have brought you nothing that is new. If I have impelled you as gastro-enterologists to warn your colleagues in other branches of medicine to remember the duodenum, this paper is justified.

DISCUSSION

DR. RALPH C. BROWN (Chicago, Ill.): Dr. Mixter has made a valuable and timely contribution, for I am sure that not sufficient emphasis has been laid upon the frequency with which pain in the mid-dorsal region, and often very severe pain, may be caused by peptic and especially duodenal ulcer.

There are certain duodenal ulcers which are not easily recognizable by X-ray, and it is possible that it is precisely this type which because of its anatomical relationships is most likely to involve the pancreas. I refer to lesions far out at the tip of the cap where the first portion of the duodenum so often turns abruptly downward and backward. The flouroscopist sees a large, well filled, symmetrical cap, but unless he uses great care, may overlook the canalization existing at the flexure, just where it turns down. If the clinician is not at hand with strong clinical evidence of ulcer, a lesion so situated may easily escape X-ray recognition.

A case in point was referred for diagnosis by one of the ablest internists in Michigan. The clinical picture was that of ulcer, but a highly competent roentgenologist could find no evidence of ulcer. Pain in the back led to a tentative diagnosis of gall bladder disease. Operation was advised, but the surgeon was reluctant, on the evidence, to operate. Our roentgenologist at the Presbyterian Hospital also missed the lesion at his first examination, the cap appearing perfectly normal. However, clinically the man had duodenal ulcer with a marked degree of pyloric obstruction, our evidence being gained by the fact that during the night time he had such severe pain that we were forced to empty his stomach and secured very large amounts of retained food, and at operation an inflammatory mass about the ulcer the size of an egg was found, involving the pancreas, illustrating the extent of pathology that may exist in a case where two or three highly competent roentgenologists had failed to recognize *the ulcer.*

Again we see, although certainly not very often, duodenal ulcer involving the pancreas, causing severe pain which *originates* in the mid-dorsal area, and, while it may radiate to the abdomen, is localized by the patient chiefly in the back.

I recently saw a striking instance of this, a case I had seen in consultation with Dr. Herrick some twelve years ago. The patient was gastro-enterostomized eight years ago with relief for one year, but since then for seven years she has had recurrent periods of excruciating mid-dorsal pain, high mid-dorsal, occurring with clock-like regularity in relation to food-taking. This was believed by one of my colleagues, for whom I have the utmost respect as an internist, to be on the basis of a spinal arthritis. More recently she has had not only complete relief, but also has been in an excellent state of general health on sufficiently careful ulcer regime.

Fortunately, the pancreas is to a marked degree resistant to peptic digestion, but the fact that the back pain of ulcer may be related to an associated pancreatitis is shown by a case seen two years ago in a robust young man who, six months prior to my observation, had had,

as an initial ulcer experience, a formes frustes type of perforation. A typical ulcer symptom picture developed. The perforation occurred while he was on a vacation in Bermuda, and, as stated, during the succeeding weeks and months a typical epigastric ulcer type of pain developed. He also had very severe pain precisely in the left lumbar region which we found extremely difficult to interpret. This would keep him awake during all the hours of the night, and for a brief period he suffered greatly. Pyelograms and X-ray films of the kidney were negative. Because of a demonstrable duodenal obstruction due to the ulcer he was operated upon and the surgeon reported that the duodenum was shortened and bound down to the pancreas with a mass on the posterior duodenal wall. The surgical report states: "The pancreas was as wide as my three fingers, at the head, and considerably thickened." It is obvious that we could account for the left lumbar pain on the basis of a diffuse, subacute pancreatitis. The surgical diagnosis was: "Acute duodenal ulcer with acute pancreatitis."

I wish to strongly emphasize the point that an essential requisite in diagnosis in the group of ulcer cases with back pain is accurate history-taking.

DR. SARA M. JORDAN (Boston, Mass.): I think the society is to be congratulated on this idea of Dr. Jones's that we should have at this meeting a correlation of internal medicine and gastro-enterology. Dr. Mixter has just given us a paper which demonstrates the importance of back pain in gastro-enterology. In our experience at the clinic, we feel when we have a patient who has backache, that if the orthopedic, the neurological and the gynecological services are convinced that the cause of the backache is not to be found in their fields, we should investigate the gastro-intestinal tract.

We often find that backache is due to some condition in the colon, frequently just a functional condition, spasm or dilatation. I think Dr. Mixter also mentioned spasm of the colon as causing backache. We find it frequently relieved completely by the relief of the functional condition in the colon.

Low dorsal backache we have come to regard with a good deal of importance from the gastro-enterological standpoint inasmuch as we find that an ulcer either of the duodenum or of the stomach, which has involved the posterior wall and penetrated into the pancreas, is often the cause of backache and may indicate that an ulcer cannot be healed with medical measures because it involves the adjacent pancreas.

Acute Abdominal Pain from Upper Urinary Tract Lesions*

By

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ACUTE abdominal pain is often the first symptom of upper urinary tract disease. Frequently the abdominal pain and associated gastro-intestinal symptoms, though entirely renal or ureteral in origin, are so typical of the acute surgical abdomen that laparotomy is performed. This is more likely to occur if upper urinary tract symptoms are minimal or, as is often the case, completely absent.

In studying the viscero-visceral reflex that permits this 'transfer symptomotology' we are primarily concerned with two factors:

1. Conditions under which painful stimuli arise in the upper urinary tract.
2. Mechanism by which this pain is referred to abdominal cavity.

Painful stimuli from the upper urinary tract have either an intrinsic or extrinsic origin. Intrinsic stimuli arise from irritation of the vegetative nerve endings within the urinary tract; extrinsic from irritation of the cerebrospinal sensory nerve endings in the peri-urinary parietal peritoneum. Both intrinsic and extrinsic pain may masquerade as symptoms of acute intra-abdominal disease, each, however, by a different anatomical-physiological mechanism.

INTRINSIC PAIN STIMULI

Intrinsic pain can arise from the renal pelvis, renal capsule or ureter. The vegetative nerve fibres which accompany the renal blood vessels into the parenchyma apparently transmit only vaso-motor and not pain impulses. We know surgically that, when operating under local anaesthesia, we can incise the kidney parenchyma without causing pain. We also know that *ordinary* stimulation of the capsule, pelvis or ureter does not cause any sensation. This, of course, is true of all tissues which are innervated by the autonomic nervous system in contradistinction to those tissues innervated by the cerebro-spinal system. Painful stimuli, however, do arise: (1) if the renal pelvis or ureter are suddenly distended due to urinary obstruction, (2) if the renal capsule is suddenly distended due to parenchymal swelling, (3) if the renal capsule is involved in an acute or sclerotic inflammatory process. If distension of the renal pelvis, ureter or capsule be gradual pain usually does not occur.

These intrinsic painful stimuli are mediated through the visceral afferent fibres which traverse the renal plexus. In man the renal plexus is composed principally of branches from the coeliac ganglion which in turn receives connections from the vagus and splanchnic and also from the superior mesenteric ganglion and aortic plexus. Jost was able to demonstrate in the rabbit a definite connection between the abdominal sympathetics and the renal plexus and this connection was clearly shown in man by the careful anatomical dissections of Hirt. In addition, the splanchnic minor always sends a direct branch to the kidney—the post-renal nerve (Henle). We see, there-

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From the Department of Urology Hospital of the University of Pennsylvania.

fore, that, through the sympathetic system, the upper urinary tract enjoys direct nervous contiguity with the gastro-intestinal tract. Kölliker and later Langley have proven histologically that the sympathetic system contains afferent senory fibres. The actual viscero-visceral reflex of intrinsic pain transfer from the upper urinary tract to the gastro-intestinal tract occurs in the spinal cord but, differing from viscero-sensory and viscero-motor reflexes, the irradiation is not confined to one segment but is transmitted through the entire cord and brain stem. This multi-segmental cord irradiation explains the variegated systemic manifestations of upper urinary tract pain.

We must consider the entire question of upper urinary tract symptomotology not from a standpoint of individual disease entities but from that of system-physiology. Any pathological process may produce intrinsic pain stimuli if any of the three pre-requisites already outlined are satisfied; any pathological process may remain symptom-free if they are not satisfied. Thus we may have slow-growing stones completely filling both renal pelves and causing great impairment of kidney function without ever producing intrinsic pain. We also see the severest renal colic resulting from temporary blockage by a minute stone fragment dislodged from the renal papilla.

We must also consider the question of pain transfer to the gastro-intestinal tract in the same manner. There are anatomical, physiological reasons and clinical data to support the statement that any lesion of the upper urinary tract which produces intrinsic pain stimuli may be referred by means of a viscero-visceral cord reflex through the sympathetic system to the abdominal cavity as indefinite non-localizable pain. Considering the fact that in this pain transfer to the abdominal cavity, true upper urinary tract symptoms may be minimal or absent, we should accept as a diagnostic necessity the urographic examination in all cases of abdominal pain which is not explained by definite intra-abdominal pathology.

This diagnostic axiom, however, is even more applicable to those cases of upper urinary tract disease causing extrinsic pain stimuli. Let us consider this more in detail.

EXTRINSIC PAIN STIMULI

As already mentioned, painful stimuli from the upper urinary tract can also arise from irritation of the sensory nerve endings in the parietal peritoneum by peri-renal, peri-pelvic or peri-ureteral inflammation. Whereas the visceral layer and serous surface of the parietal layer of the peritoneum are insensitive, the outer surface of the parietal layer is abundantly supplied by sensory cerebro-spinal nerve fibres.

Chronic infectious processes of the peri-pelvic or peri-ureteral structures do not, as a rule, sufficiently irritate the sensory nerve endings in the parietal peritoneum to cause pain. An exception to this, however, occurs in chronic perinephritis, particularly in the sclerotic type associated with the contracted pyelonephritic kidney.

Often, however, a chronic peri-pelvic or peri-ureteral inflammation is the deciding factor as to whether sufficient acute distension will result from a renal ptosis to cause painful stimuli to arise from the intrinsic vegetative nerve endings. In this case the pain would be entirely of the intrinsic variety.

Typical extrinsic pain practically always occurs if the peri-renal, peri-pelvic or peri-ureteral inflammation is acute or sub-acute in character. We have known clinically that acute perinephritis or peripyelitis produces pain which does not radiate and which the patient can always definitely localize to the renal region. This same localization of the pain occurs in acute or sub-acute peri-ureteritis.

It is this peri-ureteral syndrome that simulates, more than any other lesion of the upper urinary tract, acute inflammatory or obstructive gastro-intestinal disease. Capps has shown that stimulation of the parietal peritoneum gives rise to direct pain which is accurately localized by the patient at the site of irritation. It is this accurate localization which distinguishes extrinsic from intrinsic upper urinary tract pain. It is the location of the peri-ureteral inflammation which determines whether the pain resembles that arising from acute disease of the right or left upper abdomen or right or left lower abdomen.

To illustrate this, we have selected the following cases of peri-ureteral inflammation for presentation because in each case the outstanding, and for a time the only symptom was abdominal pain simulating that of the acute abdomen.

It is impossible, however, by urogram alone, to diagnose an acute or sub-acute peri-ureteritis. Roentgenologically there are the same findings as in a chronic peri-ureteritis plus the clinical evidence of fever and acute pain localized to the area of parietal peritoneum directly affected by the inflammatory process. On urogram, however, the following findings are significant: (1) fixation of the ureter (on more than one plate), (2) dilatation of the ureter or pelvis above the affected area, (3) impaired or absent kidney function in those cases in which a chronic peri-ureteritis slowly occluding the ureter has existed previously. When kidney function is impaired or absent, we can only obtain the roentgenological evidence of peri-ureteral pathology by retrograde pyelogram.

Case 1. Survey film of abdomen and intravenous urogram of male patient fifty-eight years of age, admitted to the hospital with diagnosis of beginning intestinal obstruction. Acute constant pain in extreme lower abdomen. Temperature 100° F. Survey film shows distension of large intestinal loops. Urogram shows poorly functioning right kidney, no visualization of right ureter, distension of left ureter to point of narrowing in extreme lower portion. History of suprapubic prostatectomy three years previously. Minimal urinary symptoms, though residual urine found to be 350 c.c. Patient treated with indwelling catheter with subsidence of acute abdominal pain within twenty-four hours. Subsequent cystoscopy revealed a definite ureteral constriction on the right side 5 cm. above ureteral orifice. Constriction also on left side at point indicated on urogram. Vesical orifice shows fibrotic contraction. Endovesical resection performed later. Acute abdominal pain relieved, however, by catheter drainage. Etiology of abdominal pain—acute exacerbation of bilateral chronic peri-ureteritis resulting from infection of adnexa.

Case 2. Intravenous urogram of female patient, age sixty-two, who was admitted into the hospital with acute pain in lower left abdomen. No urinary symptoms or signs. Slight elevation of temperature. Abdominal pain so severe that exploratory laparotomy was performed,

suspecting an acute diverticulitis. Urogram done post-operatively reveals a non-functioning left kidney. At cystoscopy it was impossible to insert catheter beyond the ureteral meatus though the meatus itself was perfectly normal. Diagnosis—acute exaceration of chronic occluding peri-ureteritis. Complete absence of kidney function. After prolonged febrile course, patient discharged symptom-free.

Case 3. Air-pyelogram revealing a ureteral constriction on the right side opposite the lower border of the fourth lumbar vertebra. Constriction due to peri-ureteritis apparently originating from within the ureter itself due to ureteral stone which, at time of cystoscopy, was pushed by the catheter to the renal pelvis. At time of admission main symptom, acute constant pain in right mid-abdomen. No history of definite lumbar pain, though patient had complained for past two years of occasional vague backache. Survey film taken because of microscopic hematuria. Acute abdominal pain due to acute peri-ureteritis at point of ureteral constriction.

Case 4. Survey film and intravenous urogram of patient admitted to hospital with diagnosis of acute appendicitis. Acute constant pain in right mid-abdomen for twenty-four hours previous to admission. History of dull, intermittent pain in same location for three months previously. No lumbar symptoms. Temperature 100-3/5° F. Urine showed moderate amount of pus cells and red blood cells. Survey film and urogram show renal stone with blockage at pelvo-ureteric junction due to peri-ureteritis, which was found at time of pyelolithotomy.

CONCLUSIONS

1. Extrinsic upper urinary tract pain due to peri-urinary inflammation may resemble the pain of the acute abdomen due to its localization at the point of irritation of the sensory cerebro-spinal nerve endings in the parietal peritoneum.

2. Intrinsic upper urinary tract pain due to irritation of the vegetative nerve endings in the renal pelvis, renal capsule, or ureter may resemble the pain of the acute abdomen due to its radiation through the sympathetic nervous system to the gastro-intestinal tract.

3. Considering the fact that in this pain transfer to the abdominal cavity, true upper urinary tract symptoms may be minimal or absent, urographic examination should be a diagnostic necessity in all cases of abdominal pain which are not explained by definite intra-abdominal pathology.

DISCUSSION

DR. LEON BLOCH (Chicago, Ill.): About six years ago I presented a paper on this subject before the Chicago Urological Society, calling attention to the fact that gastro-intestinal manifestations of urologic origin might be divided into four groups, with gastro-duodenal, biliary, colonic or appendiceal symptoms.

I shall restrict the discussion simply to that type of patient in whom the symptoms are of renal origin. One of the things we have to pay particular attention to is the finding of occasional white or red blood cells in the urine, in patients who come for gastric disturbances, because the existence of these abnormal cells in the urine should arouse our suspicions that the trouble comes, not from the gastro-intestinal, but from the genito-urinary tract.

Occasionally one encounters patients who have gastro-intestinal symptoms, in whom the urine does not show anything. An example, is the case of one of our internes who had typical symptoms of duodenal ulcer in whom, on X-ray examination, a suspicious defect was found in the duodenum, but who did not respond to treatment. The symptoms became acute and on X-ray examination of the abdomen a large kidney was found. The intravenous urography revealed a large congenital hydronephrotic kidney. Following a retrograde pylography, a temperature and chill developed.

After a nephrectomy all his gastro-intestinal symptoms disappeared. In another patient whose symptoms began acutely with very severe abdominal pain, nausea and vomiting, presumably after a meal of shellfish the night before, the diagnosis of ptomaine poisoning was made. No urine examination had been made. On the first examination in our office a few red cells were found. The patient complained of neither burning nor pain on urination.

An impacted stone in the lower end of the ureter was found on X-ray examination and when the stone was ultimately passed, he became free of all his symptoms.

Not infrequently a small stone may not be found on X-ray examination and still the patient will complain of regularly recurring distress which is sometimes very severe. An example in point is my own case. I had several attacks of renal colic and have had X-ray examinations made in several laboratories in Chicago, but no stone was ever demonstrated. It was not until after I had passed three small calculi that I became completely relieved of all my gastro-intestinal symptoms.

The important thing to remember is that in those patients in whom there are symptoms of gastro-intestinal disturbance, in whom no pathology is found in the gastro-intestinal tract on fluoroscopic and film examination, and in whom an occasional red cell or a few white blood corpuscles are found in the urine, attention should be directed to the genito-urinary tract rather than to the gastro-intestinal tract.

DR. B. B. VINCENT LYON (Philadelphia, Pa.): I should like to discuss this paper of my old classmate, Dr. Randall, from a little different view in regard to silent renal pathology.

There was a gentleman whom we reported about fifteen years ago, who was then fifty, who went through a series of passings of renal calculi without much pain, merely hematuria, and the recovery in his urinary secretion of multiple small calculi. We persuaded him finally to be studied, although he was not suffering pain and we found he had a hydronephrotic kidney with numerous stones left behind.

The interesting thing in connection with that case was that he was a polycythemic. He had a blood count of about 11.4 million, Hb. 115% and a white count of about 12,000.

This was at a period when we could find nothing in the literature as to whether polycythemia was a contra-indication for major surgery. I remember we called up most of the authoritative men in Philadelphia in medicine and surgery to find out whether we could legitimately advise him to undergo operation because of polycythemia. There was no information available. The situation was explained to the patient and he was operated upon.

Now, it is interesting that he claims himself to be a Spanish Basque, and he attributed the fact that he felt no pain in the passage of renal calculi to the supposed fact that in the Spanish Basque area they are stoics, like our American Indians. He was operated on by Dr. Leon Herman, and it was a very trying operation. The right kidney was bound down in adhesions. The man should have suffered an enormous amount of pain. I was called to the hospital that evening because the nurses could not control him five or six hours after operation, and he was sitting up in bed smoking innumerable black Havana cigarettes, and he said, "Dr. Lyon, something happened. You didn't take out my kidney."

"Yes, your kidney is in the laboratory."

He said, "I don't feel any pain."

His wound healed very rapidly. He insisted on being

out of bed on the eighth day and requested his discharge from hospital. It was not granted.

That part was interesting but the effect on the polycythemia was even more interesting. Daily blood counts were carried through and immediately after operation his red blood cells began to reduce toward a normal five million, but his white blood cells went up to 260,000. We could not interpret this. Three weeks after operation the blood count showed Hb. 88%, R.B.C. 4.4 million, W.B.C. 22,800.

I have followed this gentleman now for fifteen years and there is no longer any evidence of any remaining polycythemia. His blood counts in recent years have been within normal limits.

DR. PAUL W. ASCHNER (New York, N. Y.): Mr. President, Ladies and Gentlemen: It is with great pleasure that I greet my colleagues, Dr. Randall and Dr. Hughes, of the American Urological Association, here, and who have seen fit to bring to our attention a phase of the subject of differential diagnosis in which I have been *interested for a long time.*

For many years the urologists have been attempting to educate the surgeons in the importance of excluding urinary tract pathology in all cases of unclear abdominal catastrophes. It now seems no more than fitting and proper that the gastro-enterologists should be so educated, who are very likely to see the patient before the surgeon is called in.

As Dr. Randall has properly said, we have two types of cases to deal with, the cases of acute abdominal symptoms, and the cases with subacute or chronic abdominal symptoms. As to the acute cases, they are most likely to occur in such a manner as to simulate perforated ulcer, acute cholecystitis, acute pancreatitis, and acute appendicitis, and, lastly, intestinal obstruction.

As Dr. Randall has shown, many renal lesions come about by virtue of radiation through the nerve pathways stimulating these conditions.

In the acute case it is not feasible nor practicable, to my mind, to resort to excretory urograms for the differential diagnosis. In the first place, one hesitates to give catharsis to a patient in an abdominal condition and, to get good urograms you must have good catharsis and no gas in the intestinal tract.

In the second place, one cannot dehydrate these patients, which is also esential for good urograms; so it has been my practice, where I have an acute abdominal condition in which I wish to exclude urinary tract pathology, and I think it is the safest practice, to use the cystoscope and observe whether there is good influx from the two ureters and any evidence of retention in the pelvis of the kidney or in the ureters.

In subacute cases it is true one can use the excretory urographic methods.

There are a few types of kidney lesions one is likely to forget about, which produce violent conditions, and in which the urine is absolutely negative, and in which even the cystoscopic and urographic evidence may be misleading. One of these conditions is the condition of a septic infarction of the kidney which occurs with mitral stenosis and can produce all these symptoms of acute upper abdomen.

Another type is cortical infection of the kidney with staphylococcus of a metastatic variety. Intestinal obstruction occurs in two forms in this group of cases. In one way you have a stone in the left lower ureter, producing a marked sigmoid spasm with intestinal distention, and distention of the cecum. These are frequently operated on for intestinal obstruction. Then you have the other type of cases in which there is silent renal pathology, and the patient has uremia and retrograde fecal vomiting, and these cases are not infrequently operated upon under the misapprehension of acute intestinal obstruction.

DR. BOLAND HUGHES (Philadelphia, Pa.) (closing the discussion): Perhaps a word in defense of the acute surgical abdomen would at present be appropriate and this is mentioned in connection with the etiology of acute periureteritis. We know clinically that acute periureteritis arises either, (1) extrinsically from extension of chronic infection in the adnexia, or, (2) intrinsically from ulceration of the ureteral mucosa due to the presence of a stone. On the right side of the abdomen, however, one of the principal reasons for acute periureteritis is extension of an infection from an inflamed appendix. This extension of infection from the appendix gives us all the roentgenological signs of an acute periureteritis with the clinical picture of the acute abdomen. We should amend therefore the diagnostic axiom that Dr. Randall mentioned, to say that in all cases of gastro-intestinal pain, be the case acute or chronic in character, a urogram is necessary, but in right-sided periureteritis in which the pathology and etiology is questionable, even though you have urinary signs and symptoms, removal of the appendix is the proper therapy to be employed.

Intubation Studies of the Human Small Intestine: VII. Factors Concerned in Absorption of Glucose from the Jejunum and Ileum*

By

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THE absorption of food is regarded as occurring chiefly in the small intestine. Selecting glucose as one of the simplest food substances and one which has been extensively studied in lower animals, we have attempted a quantitative study of its absorption in the jejunum and ileum of normal human subjects. This has necessitated an investigation of various aspects of the behavior of glucose in those parts of the small bowel: (a) its normal range of concentration in the small gut after a glucose meal, (b) the variations in the osmotic pressure of the intestinal contents result-

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ing from its presence, (c) the power of the intestinal mucosa to control its concentration by dilution with hypotonic fluid, (d) the motor response of the intestine to hypertonic solutions of it and (e) the effect of its concentration in the intestinal contents on the rate of absorption. Because of the diversity of the methods required for those procedures, we are presenting the material in five parts.

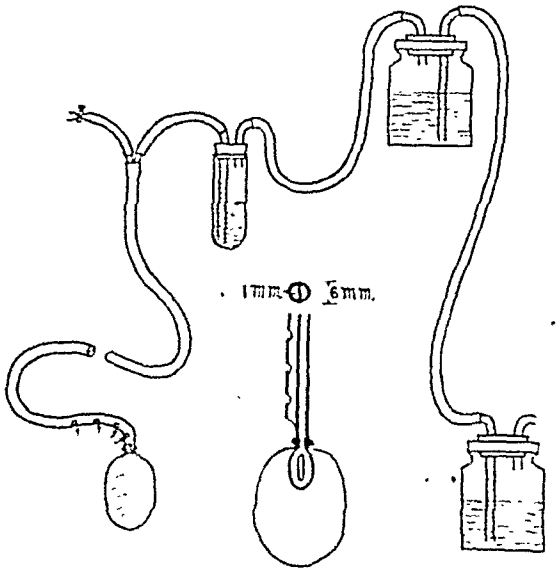


Fig. 1. *The Apparatus for Sampling Small Intestinal Contents.* The intestinal tube has a longitudinal partition giving one lumen for inflating the balloon which is done after the tube enters the duodenum to stimulate propulsive peristalsis and a second lumen through which intestinal contents are drawn up into a collecting test tube. Suction is maintained by syphon bottles usually set to give 70 cm. hydrostatic pressure.

PART I

Question: What range of glucose concentration occurs in the jejunum and ileum following its ingestion in solutions of varying strength?

Method: Using as subjects normal healthy adults and some hospital patients free from digestive disorders, we passed long rubber tubes having two lumina and a terminal balloon, by the method of Miller and Abbott (1), to selected points between the duodenum and the cecum (Fig. 1). Sugar solutions were given by mouth, and from above the balloon, which acted as a dam, intestinal contents were drawn off by constant suction. Small individual specimens were collected, which permitted a study of the rise and fall of sugar concentration at the chosen points.

The specimens were cleared by the zinc precipitation method of Somogyi (2) and after appropriate dilution were analyzed for glucose by the Benedict (3) colorimetric method.

Results: Table I gives the maximal concentrations attained at various levels of the intestine after various volumes and amounts of sugar had been ingested. This was generally less than 5 per cent.

Discussion: The drop in concentration of the glucose solution between the time of its ingestion and its subsequent recovery from the jejunum is the striking feature in these results. A far more rapid drop in concentration must, therefore, have taken place in the stomach and duodenum than we have demonstrated in the jejunum and ileum, a point which has been investigated separately (4). Since a 5.4 per cent glucose solution is isotonic with the blood plasma, the figures also raise a question as to the total osmotic pressure of these specimens which must contain, besides glucose, an appreciable electrolyte content.

PART II

Question: What is the total osmotic pressure of the small intestinal contents after glucose has been introduced (A) into the stomach, whence it may advance normally through the digestive tract and (B) into washed loops of small gut isolated from the remainder of the intestine?

A. GLUCOSE INTRODUCED INTO THE STOMACH

Method: Specimens were collected at chosen points throughout the jejunum and ileum by constant suction after the ingestion of glucose as in Part I.

The chloride and bicarbonate ions were determined as described in a preceding paper (5) in which it was also shown that in a fasting subject twice the sum of the milliequivalents of these anions was an approximate estimation of the total osmotic pressure. When this approached 300 milliosmoles it was considered to be isotonic with blood plasma. When glucose was present the number of millimoles per liter was added to twice the sum of the mEq. of chloride and bicarbonate to obtain the total osmotic pressure in milliosmoles.

Results: Table II gives the results in 13 of 20 experiments performed on 17 subjects. It will be noted that the contents of the duodenum and upper jejunum were usually hypertonic while isotonicity was maintained below these areas. Such conditions were usually found without regard to the various volumes and concentrations of the solutions ingested. Case 50 exemplifies the behavior of glucose when administered in a moderately hypertonic solution. When 250 c.c. of a 10.8 per cent solution was swallowed, the concentration of glucose in the ileum rapidly rose and slowly fell again to zero. The osmotic pressure remained close to 300 mOsM. throughout by virtue of a diminution of Cl

TABLE I

Glucose concentration in small intestine after ingestion by mouth

Subject Number	Glucose Ingested		Time of Withdrawal After Ingestion Mins.	Glucose Concentration in Per Cent	
	%	Gms.		Jejunum	Ileum
25	25	25	15-46	4.2	
52	10.8	27	18-48	.25	
140	5.4	27	18	3.3	
140	54	54	38	3.48	
141*	25	50	85	4.3	
142	25	50	27	5.5	
14	25	25	28-33		2.2
18	25	25	68-107		.11
20	25	25	55-80		1.2
22	25	25	44-73		1.0
47	50	50	30-60		1.3
50*	50	50	63-87		.07
51*	10.8	27	5-9		3.48
69	3.5	16	45-60		.22
75*	5.4	16	19-34		1.1

*Reported in detail in Table II.

TABLE II

Total osmotic pressure of intestinal contents after oral administration of glucose (experiments arranged in sequence from the proximal duodenum to the terminal ileum)

Subject Number	Solutions into Stomach			Region Aspirated	Time of Withdrawal After Ingest. Mins.	Contents Withdrawn					
	Vol. c.c.	%	Gms.			Vol. c.c.	Glucose A		Clds. B mEq.	HCO_3 C mEq.	Tot. Os. P A+2 (B+C) mOsM.
							%	mM.			
140	500	5.4	27	Duodenum	17	—	3.56	198	49	3	302
					23	—	3.98	221	35	4	300
140	100	54	54		18	—	3.50	194	85	12	388
					49	—	3.85	214	82	12	402
141	200	25	50		83	—	5.60	311	61	21	475
					115	—	3.58	199	79	16	390
142	200	25	50		96	—	5.77	320	71	8	478
					126	—	1.71	95	112	9	337
141	200	25	50	Jejunum	96	—	4.52	251	62	13	401
142	200	25	50		86	—	3.04	169	72	8	330
45	100	50	50		0-11	13	3.12	173	90	5	363
					11-16	17	3.88	216	71	5	368
					16-18	39	3.34	186	69	6	336
					18-22	13	2.76	153	71	6	307
					25-39	61	1.04	58	109	10	296
					39-65	28	.06	3	135	12	297
46	400	54	216		0-15	30	2.24	124	66	6	268
					15-30	14	5.60	311	58	11	449
					30-45	36	5.68	315	59	13	459
					45-60	20	9.11	500	56	11	640
					60-75	12	9.52	529	59	14	676
49	100	50	50		30-60	14	0		124	24	296
					60-87	29	0		122	28	300
					87-124	40	.25	14	116	24	294
					124-157	70	.02	1	114	34	297
22	100	25	25	Ileum	0-32	44	0		135	9	288
					32-48	40	.86	48	101	14	278
					48-77	44	1.02	57	104	10	285
					77-120	13	.86	48	98	8	260
50	100	50	50		0-58	96	0		97	56	306
					58-63	41	.045	3	97	57	309
					63-87	54	.073	4	98	51	302
					87-102	59	.03	2	97	50	296
51	250	10.8	27		0-5	17	1.54	86	108	5	312
					5-9	76	3.48	193	47	6	299
					9-12	54	3.20	178	50	7	292
					12-17	53	2.54	142	66	7	289
					17-30	33	.56	31	125	7	295
					30-60	84	.05	3	134	11	293
					60-90	43	0		133	12	290
75	300	5.4	16.2		0-9	29	0		145	5	300
					9-19	35	1.03	58	124	4	314
					19-34	38	1.10	61	115	4	299
					34-44	46	.134	8	125	2	282
					44-64	38	.21	12	130	3	278
					64-89	66	0		137	2	278

(Selected from 26 experiments performed upon 17 subjects).

as the glucose increased and a rise in Cl as the glucose disappeared. The bicarbonate value remained approximately the same. In certain instances the bicarbonate content was high, as in Case 50. When this occurred the Cl ion again maintained isotonicity by its reciprocal relationship. In subject 46 the extreme concentration of 9.5 per cent glucose in the jejunum indicates, however, that with sufficient glucose ingested the mechanism can be broken down.

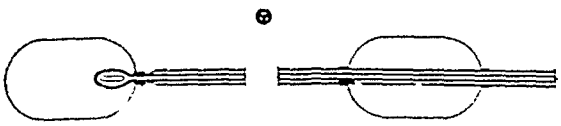


Fig. 2. *The Tube Used in Isolating Small Intestinal Loops.* The tube lumen is divided into three passages. Two lead to the balloons placed 30 cm. apart. The third leads to the gut lumen between the balloons. When these balloons are distended sufficiently to prevent the passage of material into or out of the segment of gut between them the third lumen is used to inject or withdraw test solutions.

B. GLUCOSE INTRODUCED INTO ISOLATED SMALL INTESTINAL LOOPS

Method: By the method of Abbott and Miller (6), which consists of the introduction of a three-lumened tube bearing an upper and a lower delimiting balloon 30 cm. apart, between which test solutions can be quantitatively injected and withdrawn, isolated segments of intestine were studied (Fig. 2 and 3). Into these loops glucose solutions of varying concentration were rapidly injected and after 15 minutes withdrawn.

Results: The average results of 38 experiments are shown in Chart I.

Discussion: These results, obtained after glucose was given (a) by mouth and (b) into closed segments of gut, confirm in general the observations of Groen (7) on human subjects, which showed the balance of electrolytes and glucose after the introduction of test solutions into the open small intestine above a balloon. Since he did not determine the bicarbonate content his total osmotic pressure of 275 mOsM. is somewhat below isotonicity but if the average of our bicarbonate findings is added a figure of 303 mOsM. is obtained. In the ileum the close adherence of the total osmotic pressure to approximately 300 mOsM., as shown in Table II, is very striking.

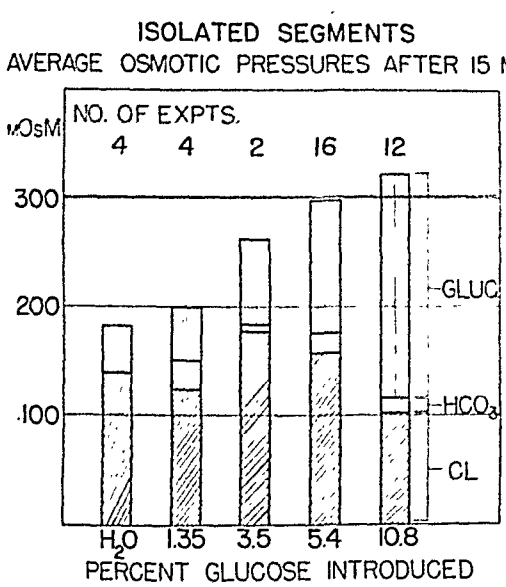


Chart I



Fig. 3. *An Isolated Small Intestinal Segment.* A roentgenogram of 30 cm. of lower jejunum isolated by inflated balloons and filled with a barium sulphate suspension.

Experiments have shown (8) that the contents of the stomach after concentrated glucose ingestion usually remain hypertonic until the stomach is nearly empty. While the stomach dilutes the sugar solution it does not continue to do so to the point of isotonicity with the blood plasma. The duodenum receiving hypertonic glucose from the stomach also remains hypertonic although the glucose concentration may be as low as 1.7 per cent while with a similar or higher concentration after isotonic glucose has been introduced into the stomach it will remain isotonic (Table II, Subject No. 140). The condition of hypertonicity may remain in the upper jejunum, but isotonicity is usually attained in the lower jejunum remaining so throughout the ileum. The maintenance of these conditions, however, implies the ability of the gut rapidly to mobilize a hypotonic fluid to dilute incoming hypertonic solutions.

PART III

Question: How rapidly can the small intestine dilute a hypertonic solution?

Method: The isolated loop technique described in Part II-B was used in this study also. Into the loops were injected 50 c.c. samples ranging from water to a 43.2 per cent glucose solution. At the end of 15 minutes the volume of each was measured.

Results: Chart II, compiled from 48 experiments, indicates that while solutions of a concentration producing an osmotic pressure below that of the blood plasma slowly lost volume, the isotonic solutions were unchanged and those of high concentration rapidly grew larger. Thus within 15 minutes solutions of twice the isotonic concen-

tration almost doubled in volume, while those of eight times isotonicity increased threefold.

Discussion: These figures give the rate at which dilution proceeds and present a picture of the role of this factor in the rapid reduction of glucose concentration in the jejunum and ileum when the solution enters in a hypertonic state. Similar results have been obtained by London and Polowzowa (9) in dogs with fistulae in the upper jejunum and lower ileum. When a 200 c.c. solution with the isolation of a segment between balloons as described in Part II-B was used. Instead of maintaining a fixed volume of air within the balloons, however, they were connected to recording instruments as formerly described (6). Hydrostatic units in the system maintained a constant pressure of 30 cm. of water which was fairly efficient in preventing leakage past the balloons and still allowed satisfactory recording. (Fig. 4). Uniform volumes of water, of 0.9 per cent NaCl and of glucose, ranging

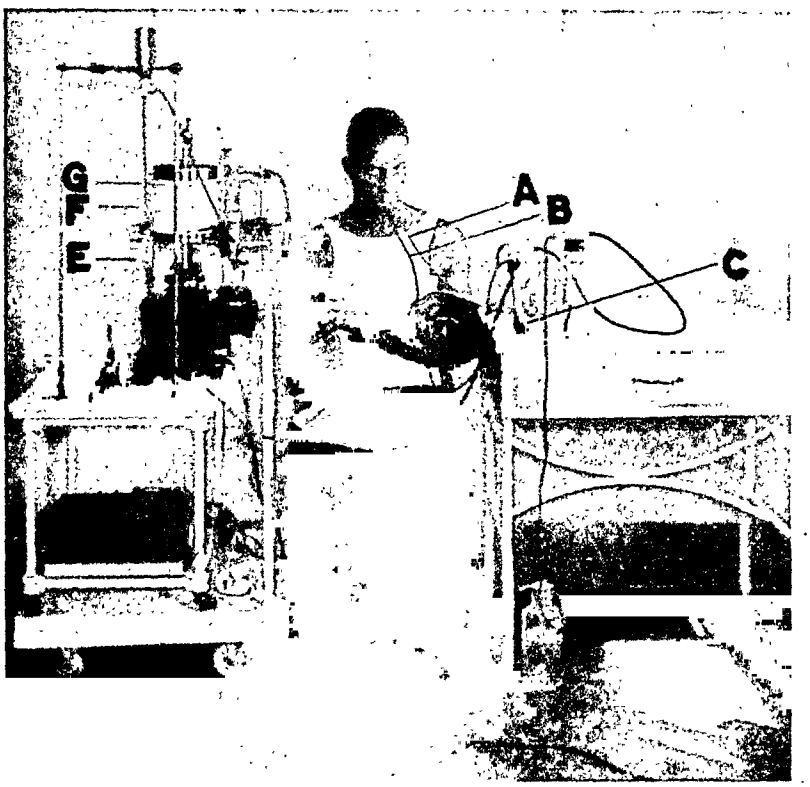


Fig. 4. *A Small Intestinal Intubation Experiment in Progress.* The subject has swallowed a gastric tube A for sampling the stomach contents and a small intestinal tube B for recovery of ileal contents C being aspirated by syphon suction D. The lumen leading to the balloon passes to a leveling bulb E which maintains a 30 cm. H_2O pressure against the intestinal wall. Contractions of the gut are recorded on the electric kymograph F. A pneumograph G detects body movements.

of 65.8 per cent was introduced in the upper fistula it gave a return of 1100 c.c. of 8.6 per cent glucose from the lower level in 110 minutes. In the duodenum, however, the rate has been shown to be even more rapid (8). The method of study, moreover, was such that if the most likely error, that of leakage of loop content, had occurred, it would have tended to give an erroneously low rate. The chance of this error increased tremendously as the concentrations used were increased until finally the method broke down completely at the highest concentrations. This suggests that the motor reactions of the bowel may likewise have a part in controlling the tonicity of the intestinal contents.

PART IV

Question: What is the motor response of the intestine to the introduction of glucose solutions of widely varying concentration as studied (a) by balloon records (b) by roentgenological methods and (c) by chemical analysis?

A. KYMOGRAPHIC STUDIES

Method: The procedure of small intestinal intubation from an isotonic solution to one of four times that concentration, were introduced.

Results: Fig. 5 gives the results of experiments considered typical for the various concentrations studied. Little difference occurred between the behavior of an empty loop and one containing 50 c.c. of water. When an isotonic glucose solution was injected there was a tendency for the loop to empty downwards as indicated by an increase in the activity of the distal balloon. When the initial concentration was doubled this activity of the distal balloon was also disturbed slightly. With four times the isotonic concentration both balloons were rapidly affected, a deep strong peristalsis being established.

B. FLUOROSCOPIC STUDIES

Method: Two subjects used repeatedly in these studies underwent a complete roentgenological study of the digestive tract by E. P. Pendergrass* and subsequently were

*We wish to express our appreciation of the many kindnesses performed by Dr. Pendergrass and his staff in assisting us with certain phases of this study.

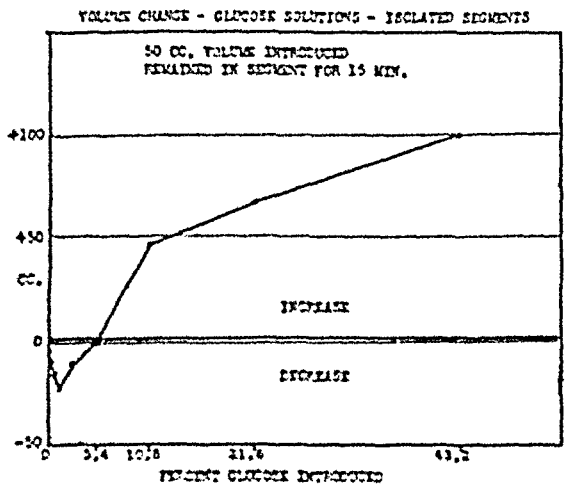


Chart II

examined again by him with a mixture of barium sulphate in 50 per cent glucose. Observations were carried out until all of the opaque material had entered the colon.

We have fluoroscopically observed the behavior of an ingested mixture of barium sulphate in 50 per cent glucose upon its initial entry into the jejunum in 11 normal students.

Results: Fig. 6. No delay in the initiation of gastric emptying or of jejunal filling was observed. The glucose meal at first advanced more rapidly than the barium alone, showing the rapid development of a haziness which is undoubtedly due, as suggested by Pendergrass, to dispersion of barium by the rapid entry of diluting fluid into the gut lumen. Later the delay in final gastric emptying and slowing of the advance of the barium-glucose meal to the colon was seen to occur at a time when the rapid influx of fluid increasing the volume of the gut contents had ceased.

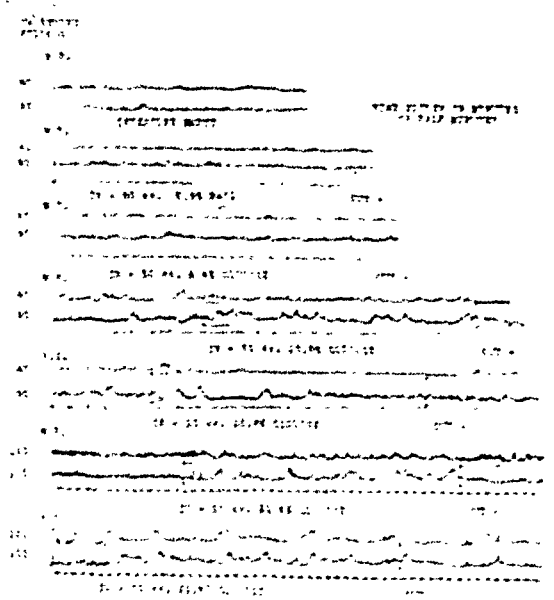


Fig. 5. *Balloon Tracings from Isolated Intestinal Segments.* These tracings were selected as 15 minute studies of the effect on intestinal activity of glucose solutions retained within the segments. The pneumograph records indicated that each subject had rested quietly throughout the experiment. With the higher concentration cramps were frequently complained of synchronously with the stronger intestinal contractions.

In the 11 cases fluoroscoped in the Gastro-Intestinal Section delay in the entry of the barium-glucose meal into the jejunum was observed only twice. In the remaining experiments the advance of the opaque material and the changes in the mucosal pattern observed were as described for the comparable period in the cases studied by *Pendergrass.*

C. CHEMICAL ANALYSIS

Method: The time of the first appearance of glucose in the recoveries made from the intestine after a glucose meal when using the two-lumened tube (Fig. 1) were recorded.

Results: Table III summarizes the data on 7 cases in which the time of the first appearance of glucose at the level under observation was accurately recorded.

Discussion: The roentgenologic findings were essentially as described under similar conditions by Pendergrass, Ravdin, Johnston and Hodies (10). The evidence yielded by all three methods is in complete agreement, showing that ingested glucose may reach the ileum in a very few minutes and that similarly a hypertonic glucose solution placed directly in the gut is rapidly dispersed. The result is to spread a thin layer of glucose in a very brief period of time over a very wide mucosal surface. Thus the motor reaction and the inflow of hypotonic fluid work together to lower the concentration of the gut contents with minimal delay. In a word all the evidence so far produced agrees in suggesting that if the absorption of glucose is to be studied it should be from solutions at or below isotonicity.

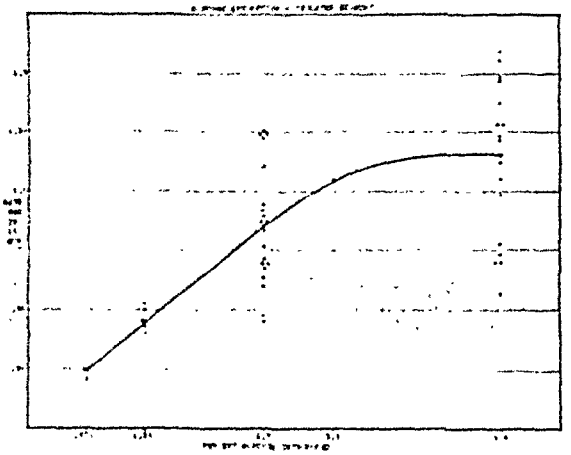


Chart III

PART V

Question: Using concentrations at or below isotonicity to reproduce the conditions normal for the small intestine, what is the relation between the concentration and the rate of absorption of glucose?

Method: Many of the observations were made by the isolated loop technique described in Part II-B. The glucose was introduced into the loop and after 15 minutes withdrawn. The loop was then washed twice with 50 c.c. volumes of tap water. The danger of error from leakage into or out of the loop being of great importance here be-

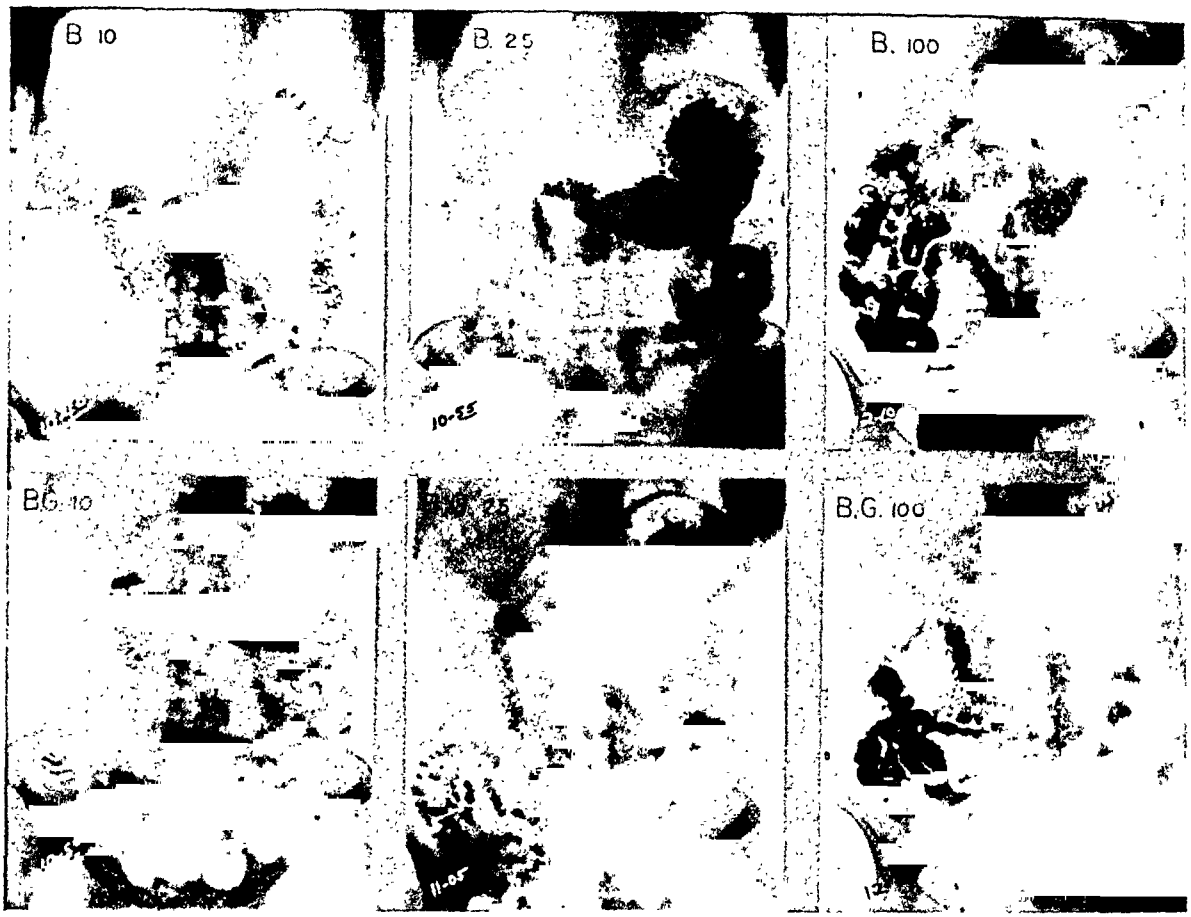


Fig. 6. *Small Intestinal Roentgenograms of Subject F. S. Showing the Effects of Glucose in the Opaque Medium.* Two studies were carried out three days apart, the first with barium in water, the second with barium in 50 per cent glucose solution. From a series of films three representative periods were selected. At 10 minutes the barium-glucose meal (B. G. 10) had advanced to a considerably greater distance than the barium meal. The haziness of the image in the advancing part of the column is due to the rapid inrush of fluid (see Part III) dispersing the barium. At 25 minutes the glucose meal is already far down the ileum, a speed of passage perhaps due to the stimulus produced by the inrushing fluid stretching the gut wall as occurs after a dose of Epsom salts. At 100 minutes when the entire tract probably contains isotonic contents the barium meal can be seen to have outrun the glucose meal. The stomach is more nearly empty and the head of the column is in the transverse colon. This is in keeping with the known actions of glucose per se prolonging gastric emptying time and inhibiting intestinal movements.

cause of absorption accounting for less than two grams of glucose at most, a second and more elaborate technique was devised. With this procedure, which differs in that it allows throughout the experiment constant aspiration of intestinal contents from immediately outside of the loop, we were in a position to detect even a trace of glucose lost past the balloons (Fig. 7). This method being more difficult to carry out was tried occasionally with each dilution studied.

Results: Chart III indicates that from approximately 0.25 to 1.5 grams of glucose are absorbed per 15 minutes from a 30 cm. loop of small intestine presented with a physiologically justifiable glucose solution. More glucose was taken up from the high concentrations than the low.

Discussion: These results imply that within the physiologically occurring range of concentration the amount of glucose absorbed increases with the concentration of the solution administered. This was shown by Omi (11) to occur in dogs when solutions of 1 to 6 per cent were used. The curve of Chart III, therefore, fills in the missing part of the curve which Verzar (12) gives for glucose absorption in relation to concentration in rats and agrees with what he supposed the shape of the curve would be had he been able to determine it. The spread of the figures at the right hand side of Chart III is interesting. Probably this is due neither to leakage past the balloons, which would have been detected (Fig. 7), nor to failure to recover glucose from the lumen of the loop, since the washes checked too evenly. It is possibly due to differences in the area of intestinal mucosa exposed between the balloons, since this is always variable and may change over a period of time as peristalsis slides the gut wall over the balloons. Roentgenological observation and tracings from balloons, however, have failed to suggest that 5.4 per cent glucose causes much pleating of the gut between the balloons. Probably, therefore, the spread of these figures is due to jejunal and ileal studies being lumped together and to the differences in size and age of the subjects. When subdivided the figures seem to suggest a greater absorption from the jejunum, though this may be due simply to the greater surface per unit length in that part as compared to the ileum, rather than to any inherent difference in the epithelial cells of the two regions.

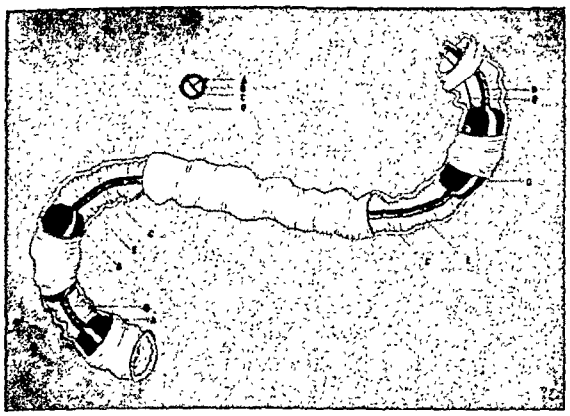


Fig. 7. *Special Three Balloon System for Isolating Intestinal Segments.* The device consists of a standard three lumened tube with a very fine single lumened tube beside it. When in the desired region of the intestine the balloons A-A are inflated through lumen A. Balloon D is inflated through tube D and the test solutions are introduced through lumen C into the isolated loop C. Suction is maintained on lumen B from before the start until after the finish of the experiment. Thus B will retrieve any of the test solution leaking out of the loop up past D or down past A and any general intestinal contents which might enter the loop from above D or below A. All experiments were considered failures in which the material collected through B contained glucose.

GENERAL DISCUSSION

The reviews dealing with carbohydrate problems written by Magee (13), Cori (14), Pierce (15) and Verzar and McDougall (16) have so completely brought the subject up to date that a further review would be a tour de force. One point of fundamental importance, however, is Cori's contention in 1925 that glucose is absorbed at a fixed rate without regard to the concentration of the solution (17). This hypothesis has at times been extended from the conditions under which he worked, that is to say with the digestive tract as a whole, to apply similarly to the small intestine alone. Ravdin, Johnston and Morrison (18) in experiments on dogs, having isolated small intestinal loops, showed that absorption increased as concentration increased, which is essentially what Part V of this study has shown for man, although in contrast to the present work they used concentrated solutions. The use of a loop isolated by balloons, however, has supplied a means of making certain observations of importance with regard to the normal physiology of glucose absorption which is not offered by the surgically isolated loop of an experimental animal. Outstanding is one's ability to withdraw intestinal contents from a given area of the small gut as fast as it reaches that point after the ingestion of a glucose meal, to isolate that area for quantitative study of absorption by a mucosal surface which up to that moment was functioning normally as an integral part of the digestive tract and, finally, to study the peristaltic response of the gut to the introduction of solutions of the concentrations normally occurring or to any that may be desirable. The evidence thus derived, when taken together, has shown that as glucose enters the gut, tonicity of the fluid is maintained by (1) a shift in the electrolyte contents, (2) the absorption of glucose, (3) an inflow of hypotonic fluid and (4) a propulsive type of peristalsis which varies in intensity with increase of concentration above isotonicity. Whether the motor response is due to mucosal irritation or to the stimulus of inpouring fluids stretching the gut, the result is a rapid dispersal of nutrient material prior to the period of depressed peristalsis (Fig. 6 BG 100) which Quigley and Phelps (19) have emphasized. Thus the intestine is equipped with a set of very effective mechanisms for disseminating and for reducing the concentration of hypertonic fluids in the shortest possible time.

From this it appears that any experiment in which hypertonic glucose solutions are placed directly in the jejunum or ileum and retained there is unphysiological. Moreover, Magee and Reid (20) have shown that hypertonic glucose solutions stop the movement of the villi, slow the blood flow through the mucosal vessels and cause an outpouring of mucus which throws a blanketing layer between the solution and the absorbing surface. Also it is apparent that due to the rapid influx of water the concentration of glucose in contact with the epithelial cells is variable and is far lower than either the mean concentration or the concentration of the fluid withdrawn.

In view of these considerations and observations elsewhere reported (4) we are led to believe that, save in extreme cases, the stomach and duodenum are able

TABLE III

Initial appearance of glucose in intestine after its oral administration

Subject Number	Solutions Into Stomach			Region Aspirated	Contents Withdrawn		First Appearance of Glucose mins
	Vol. c.c.	%	Gms.		Vol. c.c.	% Glucose	
46*	400	54	216	Upper Jej.	30	2.24	0-15
52	250	10.8	27	Lower Jej.	18	.08	16-18
25	100	25	25	Lower Jej.	15	.14	0-15
49*	100	50	50	Lower Jej.	40	.25	87-124
47	100	50	50	Mid-Ileum	15	.19	0-15
51*	250	10.8	27	Lower Ileum	17	1.54	0-5
50*	100	50	50	Lower Ileum	41	.05	58-63

*Reported in detail in Table II.

to deliver without delay a dilute solution of glucose and electrolytes to the jejunum and ileum. Thereafter the small intestine rather slowly extracts the sugar from the fluid as its contents are propelled toward the colon. If solutions that are definitely hypertonic do enter, or are placed in the jejunum and ileum a out regard to the volume or concentration of the glucose solution ingested.

2. As the stomach evacuates a concentrated glucose meal the duodenal and upper jejunal contents, although markedly diluted, usually are found to be hypertonic with regard to the body fluids, while with

TABLE I

Showing the range of absorption of glucose by the stomach after its ingestion in high concentration (37 to 43%) and the usual negligible variation of blood sugar level resulting from simultaneous duodenal stimulation. Illustrative examples

Duodenal Instillation	Total Glucose Ingested	Total Glucose Recovered	Glucose Absorbed by Stomach	Blood Sugar (mgms.) (180 c.c.)		
				Fasting	15 Min.	30 Min.
0.47% HCl	97.9 gms.	78.6 gms.	19.3 gms.	95.0	92.0	97.0
0.47% HCl	90.0 "	58.5 "	31.5 "	175.0	160.0	171.0
0.47% HCl	90.0 "	78.4 "	11.6 "	78.4	77.1	81.3
0.47% HCl	93.4 "	68.8 "	24.8 "	97.0	97.5	97.0
7% $NaHCO_3$	96.2 "	79.6 "	16.6 "	80.2	77.8	86.6
Olive Oil	86.6 "	67.0 "	19.6 "	94.0	97.0	98.0
Olive Oil	93.4 "	64.3 "	29.1 "	85.1	86.2	89.0
7% $NaHCO_3$	96.2 "	74.3 "	21.9 "	75.8	79.6	82.4
5% NaCl	92.3 "	71.4 "	20.9 "	80.2	77.2	86.1
5% NaCl	80.8 "	66.2 "	14.6 "	68.1	72.2	75.0

coordinated process of dilution and distribution in a very short time restores the fluid to about the osmotic pressure of blood plasma.

This succession of events implying as it does that the stomach and duodenum merely prepare the food for the remainder of the small intestine, while probably true for foods requiring digestion, can not be left unchallenged in the case of pure glucose. In Table I it may be seen that the major fall in concentration has already taken place before the solutions enter the jejunum. When, however, the total amount of sugar recovered from a duodeno-jejunal junction is determined (4) it proves to be but a small fraction of the total amount ingested. We must therefore assume that, in the case of a concentrated glucose solution, the stomach and duodenum play the major role in absorption. Whether this takes place in the stomach or duodenum or both is now open to question in view of the work of Holtz and Schreiber (21), Ravdin and Morrison (22) and of Shay and Cohen (23) upon gastric absorption of glucose in animal and man respectively. Thus the changes in concentration which take place above the ligament of Treitz must be looked upon not as a preparation of the chyme for jejunal and ileal absorption but in this case as an end in itself, the part played by the jejunum and ileum in absorption of glucose being of relative minor importance.

SUMMARY

1. Within wide limits the jejunal and ileal contents usually contain 5 per cent glucose or less with-

the rise and fall in the glucose content that may occur in the lower small intestine isotonicity is maintained.

3. If hypertonic solutions are placed in the small intestine the rise in volume and fall in concentration proceeds with great rapidity.

4. The propulsive activity of the small intestine increases with the concentration of glucose above 5.4 per cent in the gut contents.

5. Using solutions containing glucose in concentrations naturally occurring in the jejunum and ileum, (5 per cent or under), the rate of absorption is found to increase with the concentration.

We wish to take this opportunity of expressing our appreciation of the assistance rendered us in this study by Dr. Arthur P. L. Tsu, Dr. Alice D. Chenoweth, Dr. George Jennings and Dr. Olive D. Hoffman to whom our thanks are extended.

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TABLE II

Exp. 1. Mouth Meal 250 c.c. 39.4% Glucose

Time Min.	Stomach	Duod. 2nd Port.	Jejunal Fistula	Vol. at Fistula
15		13.8%	6.4%	345 c.c.
30		16.1%	7.1%	340 c.c.
45		11.9%	5.3%	210 c.c.
			Total Vol. at Fistula	895 c.c.

Exp. 2. Mouth Meal 315 c.c. 31.7% Glucose

15			3.9%	207 c.c.
30			5.1%	241 c.c.
45			4.7%	204 c.c.
60			5.7%	232 c.c.
			Total Vol. at Fistula	884 c.c.

Fasting contents collected at fistula for 30 min. period—Total Vol. 5 c.c.

Exp. 3. Mouth Meal 250 c.c. 39.2% Glucose

15			4.5%	165 c.c.
30			5.2%	206 c.c.
45			6.1%	204 c.c.
60			5.0%	231 c.c.
			Total Vol. at Fistula	806 c.c.

Gastric contents at 60 min.—154 c.c. of 10.1% glucose content. 200 c.c. gastric wash after removal of gastric contents—206 c.c. recovered containing 0.55% glucose

Exp. 4. Mouth Meal 250 c.c. 36.5% Glucose

Time Min.	Stomach Conc.	Stomach Vol.	Jejunal Fistula	Vol. at Fistula
15	25.6%	285 c.c.	3.4%	205 c.c.
30	19.4%	210 c.c.	5.4%	300 c.c.
45	9.8%	70 c.c.	6.7%	405 c.c.
60	5.5%	84 c.c.	2.5%	70 c.c.
			Total Vol. at Fistula	980 c.c.

Fasting contents collected at fistula for 30 min. period—Total Vol. 19 c.c.

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DISCUSSION

DR. JOHN L. KANTOR (New York, N. Y.): It seems to me a great pity that new things are reported so near the end of the meeting when time is short and fatigue increases.

I think this work is most fundamental, and that the avenues opened up by the new technic are so impressive that we are at last bound to learn a great deal about the small intestine.

Many years ago in reading Sherman's book on nutrition, I noticed a statement that all the calcium we need is absorbed from the duodenum. It seemed almost a weird and eerie thing that this important substance could be taken up so quickly from so small an area. Along come the authors and tell us that in the same area, and presumably at the same rate, most of the sugar is absorbed as well. At last we are beginning to have a little of the vision of what does take place in the small intestine, whereas up to now, we have been overimpressed by the functions of the stomach.

DR. THEODORE L. ALTHAUSEN (San Francisco, Calif.): Mr. Chairman, Ladies and Gentlemen: There are two points in Dr. Abbott and his collaborators' paper that deserve special comment. In the first place, the rate of absorption which has been considered by the Coris not to depend on the concentration of glucose, has been found to depend on the concentration of glucose. This question is important, and I think that the two findings do not necessarily conflict, because the Coris did their work with high concentrations of glucose (from 20 to 80 per cent), whereas Dr. Abbott and collaborators have been working with concentrations of glucose below 10 per cent. It may well be that this accounts for the difference in findings.

The second point I should like to comment on is the fact that Dr. Abbott and collaborators found that almost all of the sugar is absorbed in the duodenum. This bears on the mechanism of absorption of sugars. Sugars that are utilized in the body, chiefly glucose and galactose, are absorbed by simple diffusion which is greatly accelerated by conjugation with phosphates in the intestinal mucosa. Sugars not used in the body, such as pentoses, are absorbed only through simple diffusion. Tannhauser has recently shown that two substances serve to activate phosphatase: bile and ascorbic acid. It is very interesting that in the duodenum, a portion of the intestine where we expect to find the greatest concentration of bile, the maximum rate of absorption of glucose was found. I think this work confirms, indirectly, the phosphorylation theory of the absorption of utilizable sugars.

DR. HARRY SHAY (Philadelphia, Pa.): Mr. Chairman and Ladies and Gentlemen: I believe that the method devised by Drs. Miller and Abbott represents one of the real advances of experimental procedure for investigation of the physiology of the small intestine. It bids fair to permit them to solve many of the mysteries about this portion of the gastro-intestinal tract. It is particularly pleasing with an entirely different experimental approach to be able to confirm practically everything that Drs. Abbott, Karr and Miller have presented to us this after-

noon. Time will not permit me to touch upon all of their findings. I have selected, therefore, just one or two points I should like to stress.

(Slide) Table I. The first of these deals with the question of absorption from the stomach and upper small intestine. This slide is taken from some of our data concerned with absorption of glucose by the stomach. The second column represents the amount of glucose ingested. The pylorus in these cases was shut down completely by the duodenal instillation of the various substances listed in column one.

After a half hour we were able to recover from the stomach amounts of glucose shown in column three, while column four represents the quantity of glucose absorbed by the stomach during that interval.

We assured ourselves that none of the glucose had passed the pylorus, in two ways: In the first place, the glucose meal was mixed with barium, and frequent and careful roentgen examinations were made for barium beyond the pylorus, secondly, for five minutes during each of the fifteen-minute periods of observation, the duodenal contents were removed and the material tested for glucose; with the high concentrations of glucose in the stomach, we felt that negative duodenal reactions for glucose gave additional proof that none of the glucose had passed the pylorus.

Incidentally, we studied gastric absorption of glucose in dogs by mechanically closing off the pylorus, and we found that this sugar in high concentration was absorbed from the dog's stomach in amounts varying from 11 to 18 grams in one hour. The stomach was completely removed at the end of these experiments and all the gastric contents carefully recovered.

(Slide 2) Three years ago we had the opportunity to study a patient who had a high jejunal fistula, produced quite by accident. This man had had intestinal obstruction seven years before. Apparently so much distention had been present at the time of operation that the surgeon did a jejunostomy instead of an ileostomy as intended.

Through this jejunostomy we fixed a rectal tube held in place by a balloon and were thus able to collect the material from the proximal jejunum. In some experiments we intubated the duodenum in the usual manner as well and were able to collect specimens simultaneously from both areas. We administered various meals by mouth. In the first experiments we found that after a 250 c.c. meal of 29.4% glucose, we recovered from the duodenum after fifteen minutes, a concentration of glucose of 13.8%, in the next fifteen minutes 16.1%, and at 45 minutes 11.9%, while from the jejunal fistula the glucose recovered during the same intervals ran 6.6, 7.1, and 5.3%. I should like to call your attention to the volumes recovered in the first fifteen minutes, 345 c.c. and 340, and so forth, a total of 895 c.c. collected in 45 minutes from the fistula when only 250 c.c. had been given by mouth on an empty stomach.

Experiment 2 shows essentially the same low concentrations of glucose in the jejunum that Dr. Abbott has pointed out. Again the large volume collected from the jejunum after a meal of 31.7% glucose, in spite of the fact that for thirty minutes before the experiment was started, the collection from the jejunal fistula was only 5 c.c. Here we would like to draw attention to the difference in the amount of fluid probably added by the stomach, on the one hand, and the duodenum and upper jejunum on the other. In Experiment 4, fifteen minutes after 250 c.c. of 36.5% glucose had been given by mouth, 285 c.c. were recovered from the stomach. From the jejunal fistula we obtained 205 c.c. of a 3.4% glucose solution during that period.

We are inclined to believe from experiments of this type that in the human stomach, glucose solutions of high concentration are readily absorbed and that dilution plays a less important role than it does in the duodenum and upper jejunum. With a concentration of glucose of 25.6% in the stomach, (Experiment 4) at which concentration the stomach, we know, could not be emptying rapidly. At this point only 285 c.c. of fluid were present, yet through the fistula we obtained 205 c.c. The same holds true for the next 15 minute period. At this point with a 19.4% solution and a 210 c.c. gastric volume, 300 c.c. had come through the jejunal fistula. This indicates to us that in high concentration the stomach absorbs glucose quite rapidly and while the jejunum does, also, its chief function seems to be to dilute the glucose and bring it to isotonic conditions for admission to the jejunum, as Dr. Abbott has pointed out.

Deposition of Glycogen in Normal and in Experimentally Damaged Livers After Oral and Intravenous Administration of Dextrose*

By

T. L. ALTHAUSEN, M.D.†

With the Technical Assistance of

M. STOCKHOLM, M.A.

SAN FRANCISCO, CALIFORNIA

THERE are several reasons why the comparative merits of oral and of intravenous administration of dextrose deserve investigation by modern experimental means. First, dextrose is used more and more extensively in treatment especially of diseases of the liver. Second, there is difference of opinion as to whether the oral or the intravenous method is more effective for therapeutic administration of dextrose. Third, in experiments to determine the comparative deposition of hepatic glycogen after oral and after intravenous administration of sugar, normal animals have been used almost exclusively. Since the author has found (1) previously that in animals damage to the liver influences the response of hepatic glycogen to administration of insulin and dextrose, there is a possibility that injury to the liver may influence also the effectiveness of the two methods of administration. Fourth, the reported experiments which have

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than that which had been anticipated at the beginning of this work, and that a significant excretion of sugar took place in rats that were given dextrose intravenously. For this reason a second experiment was conducted with normal rats and with rats receiving 6 mg. of phosphorus per kg. of body-weight in which corrections for these factors were introduced. In order to equalize the amounts of dextrose actually utilized in the body after oral and after intravenous administration the rats receiving sugar by stomach-tube were done first. After the average amount of dextrose absorbed by these animals in 3 hours was ascertained the rats receiving dextrose intravenously were given in 6 equal doses the same amount of sugar plus the average amount excreted by similar animals in the first experiment. In the final calculation of the utilized amounts of dextrose the urinary excretion of sugar by the same rats was taken into account.

A third experiment was performed in order to test the effect of maximal doses of dextrose on the glycogen content of damaged livers. In this experiment, rats treated with 6 mg. of phosphorus per kg. of body-weight were given dextrose orally as well as intravenously, and the level of their hepatic glycogen was compared to that of rats similarly treated but receiving only the oral dose of sugar.

RESULTS

Normal rats. The rats that received dextrose intravenously excreted in the urine an average of 28 ± 2 mg. of sugar per 100 gm. in 3 hours. The animals given dextrose by stomach-tube had no glycosuria.

From Table I it is seen that when care was taken to adjust the intake of dextrose in such a way that oral and intravenous administration led to the actual utilization of nearly equal amounts of this sugar in the two groups of rats, the quantity of new glycogen deposited in the liver of normal rats was the same regardless of the route by which the sugar reached the liver. Further, the method of administration of dextrose was found to have no influence on the proportion of retained sugar which was deposited as new glycogen.

In normal rats that were given intravenously a dose of sugar exceeding by 65 per cent the maximal rate of intestinal absorption the hepatic glycogen was found to be almost doubled. The fact that the proportion of retained dextrose deposited as glycogen was approximately equal in the two groups showed that the greater amount of sugar given by vein and not the method of administration accounted for the difference.

The hepatic glycogen was found to be higher in rats during the Spring than during the Fall and Winter seasons. This is a well known phenomenon.

Rats treated with phosphorus. All rats treated with phosphorus showed sluggishness of movements and loss of weight. In the group injected with 8 mg. of phosphorus per kg. of body-weight these changes were most noticeable, and in addition more than one-half of the animals receiving this dose died before the end of 48 hours after the first injection. Rarely a rat receiving 6 mg. of phosphorus per kg. of body-weight failed to survive the period of preparation for the experiment.

Grossly, the livers of rats receiving 4 mg. of phosphorus per kg. of body-weight appeared normal. The livers of the animals injected with 6 mg. of phosphorus were pale and often friable; and those of rats receiving 8 mg. of phosphorus per kg. of body-weight were yellow and very friable, and on being hydrolized with 30 per cent potassium hydroxide yielded large amounts of fat.

Sections of the livers from these animals were examined by Dr. J. F. Rinehart of our Department of Pathology to whom we are indebted for the following pathological report: The hepatic cells of rats receiving 4 mg. of phosphorus per kg. of body-weight showed a moderate infiltration of fine fat droplets within the cytoplasm, occasional small zones of necrosis with leucocytic infiltration, and small zones of hemorrhage in areas of degenerated cells. These findings indicate very definite injury to the liver. In the livers of animals injected with 6 mg. of phosphorus per kg. of body-weight the cytoplasm was overfilled with fine fat droplets and showed scattered zones of necrosis with leucocytic reaction. In the livers of rats receiving 8 mg. of phosphorus per kg. of body-weight the same changes but somewhat more marked and more widespread were noted.

Table II shows that in this experiment rats treated with phosphorus absorbed somewhat smaller amounts of dextrose from the intestine than did the normal animals. The excretion of sugar in the urine of rats receiving dextrose intravenously averaged 27 ± 3 mg. per 100 gm. of body-weight in 3 hours. Animals that were given dextrose by stomach-tube excreted no sugar. When the intravenous dose of dextrose was adjusted to equal the amount of dextrose absorbed from the intestinal tract in the other group of rats plus the amount lost through the kidneys the hepatic

TABLE II

Hepatic glycogen in normal rats and in rats treated with phosphorus after oral and after intravenous administration of dextrose in amounts equal to the maximal rate of intestinal absorption

Experimental condition	Method of administration	No. of rats	Range of weight after fasting 24 hours	Dextrose given in 3 hours per 100 gm.	Dextrose utilized in 3 hours per 100 gm.	Standard deviation	Hepatic glycogen per 100 gm. of body weight	Standard deviation	% of dextrose deposited as new glycogen
Normal	Oral	16	Gm. 210-300	Mg. 600	Mg. 366	39	Mg. 53.0	14	13.9
	Intravenous	15	218-335	405	376	5	55.7	19	14.3
Phosphorus poisoning 6 Mg. per Kg.	Oral	8	122-160	600	323	22	48.0	11	15.1
	Intravenous	9	130-160	351	324	6	48.0	6	14.8

reported finding in human beings (9) that even the seriously injured liver does not lose its ability to acquire glycogen when an excess of sugar is available in the body. However, when an extreme degree of injury was inflicted on the liver by doses of phosphorus, which proved fatal within 48 hours to over

On the other hand, the importance of this observation of ours on normal rats is diminished by the fact that when animals with damaged livers were made to utilize amounts of dextrose which were more than double the maximal rate of intestinal absorption the additional increase in hepatic glycogen was statisti-

TABLE IV

Hepatic glycogen in rats treated with 6 mg. of phosphorus per kg. of body-weight after oral and after combined oral and intravenous administration of dextrose.

Method of administration	No. of rats	Range of weight after fasting 24 hours	Dextrose absorbed in 3 hours per 100 gm.	Dextrose injected intravenously in 3 hours per 100 gm.	Dextrose excreted in the urine in 3 hours per 100 gm.	Dextrose utilized in 3 hours per 100 gm.	Hepatic glycogen per 100 gm. of body weight	Standard deviation	% of dextrose deposited as new glycogen
Oral	5	Gm. 212-285	Mg. 278	Mg. —	Mg. —	Mg. 278	Mg. 42.0	15	15.1
Oral and intravenous	5	210-286	313	400	86	627	53.6	17	8.5

one-half of the rats this organ failed to increase its content of glycogen with the amounts of dextrose administered in our experiment regardless of the method of administration.

The equal effectiveness of both ways of giving dextrose to animals with normal and with damaged livers was also shown in our experiments by the approximately equal proportion of administered sugar which was retained in the liver as glycogen regardless of the route by which the sugar was given.

In so far as experimental findings in animals can be applied to therapeutic procedures in human beings our results indicate that the method of administration of dextrose for diseases of the liver is a matter of convenience. Consequently the giving of dextrose by mouth is preferable unless vomiting or other contraindications to the use of the oral route are present. Administration of dextrose remains indicated even in the severest forms of hepatic disease, when from analogy with our experiments with phosphorus apparently no deposition of hepatic glycogen is possible, in order to prevent dysfunction of other important organs, such as the heart, from want of sugar due to impairment of gluconeogenesis on the part of the liver.

When normal rats were given more sugar intravenously than they could absorb in 3 hours from the alimentary tract, the glycogen content of the liver rose in proportion to the added amount of sugar. This was confirmed by the unchanged proportion of dextrose converted into hepatic glycogen. Apparently within certain limits, in normal rats the newly formed glycogen of the liver is proportional to the total amount of sugar entering the body even when the latter exceeds the maximal rate of intestinal absorption. This suggests intravenous in addition to oral administration of dextrose in patients with severe hepatic damage. Such a procedure seems also attractive in view of the work of Woodyat, Sansum and Wilder (10) who showed that normal persons are able to utilize without glycosuria about 850 mg. of dextrose per kg. of body-weight per hour for periods up to 12 hours, while estimates of the maximal rate of intestinal absorption in man indicate that only about one-fifth of this amount can enter the body from the alimentary canal.

cally insignificant. This was shown to be true also by the progressively smaller proportion of dextrose deposited as glycogen which declined to about one-half of the normal figure when the amount of dextrose entering the blood stream was doubled (Table IV). We interpret these observations as indicating the existence of a limit which varies according to species and degree of hepatic damage and above which even the administration of a large excess of sugar is unable to increase the glycogen of the liver. Such a limit appears to be reached in rats under our experimental conditions when amounts of dextrose approximately equalling the maximal rate of intestinal absorption are given.

SUMMARY

1. Dextrose was administered to one group of rats by stomach-tube and to another group by intravenous injection. Determinations of hepatic glycogen were made three hours after giving the sugar. Control experiments with water and saline solution were performed.

2. In normal rats and rats with hepatic damage produced by injections of phosphorus, oral or intravenous administration of equal amounts of dextrose led to an approximately equal deposition of glycogen in the liver.

3. In animals with extreme damage to the liver, very little glycogen was deposited when either method was used.

4. By increasing the amount of dextrose given intravenously above the maximal rate of intestinal absorption, the deposition of glycogen in normal rats was increased. Under similar conditions in animals with hepatic damage, the increase in glycogen was insignificant.

5. The application of this study to the treatment of diseases of the liver with dextrose is discussed.

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DISCUSSION

DR. VICTOR C. MYERS (Cleveland, Ohio): Mr. Chairman and Members of the Association: It is quite natural that this Association should be vitally interested in the function of the liver, since this organ is the reservoir and storehouse for materials, both foods and poisons, taken up from the intestinal tract. As first pointed out by Claude Bernard, in his great period of activity between 1850 and 1860, the liver under normal conditions serves as a balance wheel in regulating the metabolism of carbohydrates. The preëminent role that the liver plays in regulating carbohydrate metabolism, however, was not recognized until a few years ago, when Frank Mann and his associates at Rochester discovered that after the extirpation of the liver, dogs died from hypoglycemia. Having recognized this fact, he found it possible to elucidate many of the liver's functions, since he was not able to keep his dogs alive a reasonable length of time by intravenous glucose therapy.

With this background, Dr. Althausen has made many studies on the influence of the liver and the mobilization of glucose, and the storage of glycogen, his present report being the latest. It seems to me his studies on the deposition of liver glycogen particularly deserve commendation. This is a function of the liver which can be accurately measured and in consequence, one can make interpretations about the utilization of glucose. From blood sugar tolerance curves alone, one's interpretation may obviously be incorrect.

One should do as Dr. Althausen and the Coris have done, carry out studies on small animals, such as the white rat. It is then possible to sacrifice the animals and determine the glycogen and thus get an exact determination of this important function. It is evident from the charts that Dr. Althausen showed on the screen, that in severe liver damage from phosphorus poison, the ability to deposit glycogen is markedly impaired.

He has emphasized the value of sugar therapy in liver disease in a previous paper, and his latest conclusion seems logical, namely, that if one is going to give glucose therapy, the simplest, and easiest way, and the most practical way, is to give it by mouth.

How is the glucose deposited in the liver as glycogen? How is the glycogen broken down in the liver to glucose when the body needs it? We know as a result of the work of Claude Bernard, to which I have already referred, that in the normal individual, glucose content of the blood is kept constant, pretty close to 0.1 per cent in the blood. It has always seemed to me that the probability was pretty good that this transformation was carried out under the action of a diastatic enzyme, perhaps one that has a reversible action.

We know in the digestion of starch in the alimentary tract it is broken down by enzyme action to glucose in which form it is absorbed. It seems perfectly logical that some similar mechanism may exist for the building up of this monosaccharide to glycogen in which form it is stored for relatively immediate use.

We know that if we collect blood and allow it to stand a short time, some of that glucose goes over to lactic acid and we have a fall in the sugar concentration of the blood. This is due apparently to an enzyme that is present in the leukocytes.

We also know that a diastatic ferment is present in the blood. Some years ago Dr. Killian and I carried out a study on the diastatic activity of the blood in normal individuals, diabetics, and other conditions, and found that the diastatic activity of the blood was quite markedly increased in diabetes. This was before the discovery of insulin.

More recently Dr. Eric Reid, sent to my laboratory from Aberdeen by Dr. J. J. Macleod, repeated this work with the same findings that Dr. Killian and I got in 1916. He also found that the diastatic activity was reduced to normal in the diabetic by the administration of insulin.

We thought when insulin was discovered that we would very soon be able to reveal the mechanism by which energy was obtained from carbohydrate, but we really do not know much more now than we did then. We know that insulin will enable a diabetic to burn carbohydrate in the normal manner, but we cannot go very far beyond this. Through some work that Dr. Reid and I carried out in cooperation with Dr. Quigley, on dogs, we came to the theoretical conclusion that probably the insulin acts in some way upon the diastatic activity of the blood through the liver.

I personally believe before this story is completely elucidated that we need to have some information upon the chemical mechanism upon which Dr. Althausen has made pathological studies. To be sure one can recognize liver pathology under the microscope, but, after all, being a biochemist, I feel that the things that one cannot see, which are producing the changes there, are a great deal more important than the things one actually sees with the microscope.

I do not know that I can suggest to Dr. Althausen how I would begin such a study, since every effort I have made with studies on the diastatic activity of the liver has been unfruitful, but I thoroughly believe in the remarks that I have made in this connection. Observations have been made in recent years that throw an entirely different interpretation upon the utilization of glucose. We know that in the muscle, for example, the immediate source of energy apparently is phosphocreatine, and that its break down furnishes the energy. Then there is a resynthesis of the phosphocreatine at the expense of adenosin triphosphate, and apparently resynthesis of this compound occurs at the expense of hexophosphate.

Recently Dr. Tannhauser made a rather interesting analogy in this connection that rather amused me. He suggested that phosphoric acid acted in this particular case like a basketball player. First it would catch the glucose, then the adenylic acid, and finally the creatine, and then the process would be repeated. Through some mechanism such as this, apparently, glucose indirectly furnishes energy for muscular action. Although this is a little remote from the problem in question, it is extremely important since the liver is very vitally concerned here, as it is the organ that keeps the flow of glucose constant.

Galactose has been used for a long time as a functional liver test, ever since Bauer discovered in certain cases of cirrhosal liver that galactose was excreted after the ingestion of milk.

It seems to me it would be interesting if Dr. Althausen would continue his work, also using galactose and fructose with his rats. As I recall, according to Dr. Cori, although galactose is well utilized, it is not quickly converted to glycogen in the liver. I believe that perhaps something interesting might come out of further studies.

Dr. Althausen is to be congratulated upon this study and I believe that although sometimes the topic appears devoid of all clinical interest, the first thing we know there is a practical application that wasn't at all apparent when the work was begun.

DR. FRANKLIN W. WHITE (Boston, Mass.): There is one practical and important side of this work of Dr. Althausen's which he may have been too modest to stress. He has shown the importance of glucose in protecting the sick liver cell in laboratory animals. Let us take this information into the hospital wards: When we have a sick liver case with jaundice, vomiting and drowsiness, we must use intravenous glucose; but later on when this patient is no longer drowsy and nauseated but is getting better and is able to take liquids and food by mouth, I notice that the house officers are quite likely to carry on the *intravenous* glucose medication with the feeling that there is something mysterious or especially useful about giving it in an intravenous way, perhaps with the idea that a greater percentage is absorbed or utilized. Now that Dr. Althausen has shown (if I have interpreted his figures aright) that when the patient is able to take it and it can be given by mouth, it is utilized just as well as if given by the intravenous method; we have information which saves a great deal of time and trouble and does the patient just as much good.

DR. THEODORE L. ALTHAUSEN (San Francisco, Calif.) (closing the discussion): I merely want to thank the people who discussed my paper and I think that it does have a clinical application, as Dr. White has said.

Editorials

DISSOCIATION OF BACTERIA

ADAMI (Brit. Med. Jour., 2:1215, 1898) contended that bacteria were constantly invading the body from the gastro-intestinal tract. He contrasted the organ cultures as determined by bacteriological technic with the histological examinations and concluded that many bacteria were present but few were able to grow. Adami's co-worker Ford (Jour. of Hyg., 1:277, 1901) examined tissues from normal animals and found three-fourths of the cultures positive after three weeks' incubation. He was unable to grow these forms in subcultures.

Florey (Jour. Path. and Bact., 37:283, 1933) describes the fate of bacteria when brought in contact with the intestinal mucosa. When B. aertryche is introduced, in the form of a thick suspension into an intestinal loop in a guinea pig, there is a considerable exudation of phagocytic cells into the intestinal lumen, and in places the epithelial cells desquamate leaving bare the underlying stroma. The detailed study of paraffin sections, appropriately stained, indicated that the bacteria not infrequently enter the epithelial cells themselves. These intracellular bacteria in many, but not in all cases, show signs of degeneration. The invaded epithelial cells show no histological evidence of death. How the bacteria gain entrance to the cells is uncertain, but it does not seem to be through any phagocytic activity, as usually conceived, since inert particles or non-pathogenic bacteria remain in the lumen of the intestine.

Gulbrandsen (Amer. Jour. of Hyg., 22, No. 2:257, 1935) cultured the organs from normal dogs, guinea pigs, rabbits and rats in broth. He found a slight clouding at the bottom of the tubes or flasks after incubation. Stained smears revealed a pleomorphic type of bacteria present. He could not obtain growths from these primary cultures on any media. In as much as almost all normal tissue gave these results, it was impossible to determine if living tissue was necessary for their work.

Gulbrandsen resorted to the use of mature guinea pig fetuses delivered by caesarean section. The organs of such animals were sterile of this pleomorphic flora. Bacteria were fed by mouth to these full term sterile guinea pigs and organ cultures made fifteen to sixty minutes later. B. typhosus, B. paratyphosus, B. Staphylococcus aureus and B. diphtheriae were the bacteria used for oral feeding. Pleomorphic bacteria could be demonstrated in the organs of these young animals fifteen minutes after feeding of the living cultures. These resembled the forms found in adult animals. These pleomorphic bacteria are non-antigenic and biochemically inactive. B. typhosus or B. diphtheriae were altered in their passage through the wall of the sterile intestinal tract so as to produce a tissue growing symbiotic form of bacterial flora which was non-pathogenic.

Adami's and Ford's observations were therefore substantiated. Every bacteriologist has encountered dissociation of bacteria and many are engaged in the study of this problem. The tissue symbiotic bacteria studied by Gulbrandsen are dissociated types. Meyer and Ryan (Jour. of Lab. and Clin. Med., 22, No. 2:113, 1936) using a different technic found such types in the blood of normal persons as well as certain pathological cases.

Dissociation seems to be one of the important mechanisms of defense of the body against infection by bacterial invasion. More questions are raised than answered by Gulbrandsen's work. The gastro-intestinal tract is indeed a complex biological environment for microorganisms.

Lloyd Arnold, Chicago, Ill.

BILIRUBINEMIA

AS ROUS and Drury demonstrated some years ago, the degree of bilirubinemia in animals which have been subjected to experimental biliary obstruction is a direct expression of the physiologic wastage of corpuscles; anyone who has noted the deepening of jaundice after transfusion or its fading after hemorrhage can confirm this observation. In cases in which human beings have jaundice there are two additional factors which modify the degree of bilirubinemia, namely, the completeness of mechanical blocking of the bile passages and the degree of parenchymal injury of the liver. The question naturally arises as to whether there are, or will be, methods by which these three factors can be distinguished from each other. To approach the subject, one may first consider the two types of bilirubin found in the blood, that is, the indirect-reacting type which is normally present and which exists in increased quantities in the hemolytic forms of jaundice, and the direct-re-



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acting type, the presence of which characterizes the obstructive and hepatogenous forms of jaundice. Rich has designated as "retention jaundice" those types in which there are indirect van den Bergh reactions and acholuria and has characterized those types in which there are direct-reacting bilirubin and bile in the urine as "regurgitation" jaundice. The inference of this classification is obvious.

Exactly what chemical differences exist between these two types of bilirubin is still unknown; one theory holds that bile acids, which are presumably present in excess in the blood of patients who have obstructive or hepatogenous jaundice, lower the surface tension of the bilirubin molecule and thus change its chemical behavior. Another theory is based on the assumption that indirect-reacting bilirubin is in combination with protein which retards the direct van den Bergh reaction and inhibits renal filtration. Supporters of this view hold that passage of indirect-reacting bilirubin through the hepatic cells removes this combined protein and leaves the "regurgitated" bilirubin in a form free to pass the kidney and alter in color when Ehrlich's diazo reagent is added to the serum. The recent studies of Duesberg lend support to the latter hypothesis; his observations indicate that in the degradation of hemoglobin iron is first split off while the globin fraction remains in combination as far as the formation of bilirubin.

Is all of the bilirubin present in the blood of patients with obstructive or hepatogenous jaundice in the direct-reacting form? That is, has it all passed through the cells of the liver and been regurgitated into the blood stream? If current conceptions of dysfunction of the cells of the liver in the presence of obstruction or toxic injury are correct, this should not be the case, but part of the bilirubin in the circulation should be the indirect-reacting form which is produced by physiologic wastage of corpuscles and dammed back into the circulation because of the physiologic or pathologic inability of the hepatic cells to take it up. The photolometric studies recently reported by Osterberg appear to indicate that a part of the circulating bilirubin in cases in which jaundice is due to mechanical obstruction and parenchymatous lesions of the liver gives an indirect reaction, while another fraction apparently has passed through the liver cell, as shown by a direct van den Bergh reaction. While further chemical and spectrophotometric studies of differences existing between directly and indirectly reacting bilirubin will doubtless be required to establish the authenticity of these methods, it does seem clear that the quantitative determination of the two forms of bilirubin in a single specimen of serum is not beyond the bounds of possibility. Such information when it becomes available will probably be of considerable clinical importance. It may be that the amount of one or the other types of bilirubin present in the individual case is of prognostic significance and may give information which the total figures, now in use, do not supply. These and similar studies naturally will lead to some revision of present views regarding the mechanics of "regurgitation" jaundice; they emphasize the importance of learning what disposition is made of the porphyrin and iron-containing complement of the hemoglobin molecule, and, finally, they indicate that the complexity of the problem of bilirubinemia increases as more is learned of its essential chemical nature.

Albert M. Snell, Rochester, Minn.

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THE ETIOLOGY OF PEPTIC ULCER

A NEW statement on the etiology of ulcer is possible in the light of recent developments in gastric physiology. Mann's experimental production of ulcer, now widely confirmed, showed the paramount importance of the acid factor in the immediate causation of ulcer in dogs. There is good evidence of a similar mechanism in man. Experience with really continuous, night and day, neutralization of gastric acidity as by the aluminum hydroxide drip in the clinical treatment of uncomplicated ulcer indicates that Mann's experimental results may be fairly satisfactorily duplicated. That is to say, healing occurs quite regularly within one to two weeks. This would seem to establish the fact that the erosive action of acid gastric chyme is the *sine qua non of actual ulceration* and the whole immediate cause of clinical ulcer and that all others factors act as predisposing causes. From the practical standpoint the predisposing causes may be of great importance, quite overshadowing the immediate and specific cause, since, when they are removed, *the ulcer may heal spontaneously* or on account of the restoration of the normal neutralizing mechanism of duodenal regurgitation. Moreover, proved cases of peptic ulcer in proved cases of constant anacidity with histamine probably do not exist. Reports of such cases even on single examinations are so rare as to negative their significance.

Etiological factors in ulcer have usually been referred to as neurogenic, vascular, infective, toxic, glandular, traumatic and others including a mysterious X factor. The old physiological query of "why doesn't the stomach digest itself?" is probably best answered by the statement that it does when its defenses are down. The above predisposing factors lower local resistance or disturb the normal neutralizing mechanism so that acid peptic digestion occurs. A localized arterial occlusion might lead to ulcer in the stomach wall while the same process in less exposed tissues might cause no lesion or an innocent infarction. Likewise, an organic lesion in the sub-thalamic area of the brain or purely functional psychic impulses may induce vasomotor or trophic changes in the gastric mucosa with a profound lowering of local resistance. Nervous factors, which every mature clinician knows are most important in ulcer may operate in part by inducing pylorospasm and retaining acid secretions for abnormally long periods.

Such overshadowing of a specific cause by conspicious predisposing causes is not rare in medical science. For example, "traumatic arthritis" as described by

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Total: 8 ounce liquid — 75 calories

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Hilton in his "Rest and Pain," before the discovery of the tubercle bacillus quite adequately explained joint tuberculosis as the result of injury. The teaching survives to this day in the beliefs of most victims of Pott's Disease. How reluctantly even the medical profession of that day yielded to the bacterial "theory" of disease.

It is extraordinary that Sippy with his conviction upon the importance of the acid factor in ulcer did not devise a method of really continuous night and day neutralization. Ulcers apparently heal at a rate that is proportional to the constancy of neutralization. Some ulcers heal spontaneously, others heal by part time neutralization as by the Sippy routine, but the largest percentage of cures in chronic cases and in the shortest period of time is obtained by really continuous neutralization. This removes the immediate cause of ulcer and permits prompt healing. The predisposing factors should then be attended to as far as possible. This is a reversal of the process or of the sequence of events leading up to and causing ulcer. Secondary complications such as extensive cicatrization or obstruction really present a separate problem, usually surgical and play no role in the primary pathogenesis of peptic ulcer.

Meuhlengracht's remarkable reduction of mortality from hemorrhage by feeding the bleeding ulcer case liberally and by the use of alkalis is probably due to an approximately continuous neutralization and arrest of gastric motility.

Really continuous night and day aluminum hydroxide drip has been most effective in controlling persistent and recurrent bleeding. There is apparently a prompt cessation of the erosive process and of digestion of the newly formed clot in the bleeding vessel.

This conception of the etiology of ulcer has practical implications since there has been, even among gastroenterologists, a half-hearted conviction as to the importance of the acid factor and a half time use of antacids with half way results. Thorough use of continuous neutralization for prompt healing of the open lesion permits of a more rational follow-up leading to individualized treatment of the whole patient. Attention to the predisposing causes of disturbed gastric physiology is then of the first importance in the prevention of recurrences.

Vernon C. Rowland, Cleveland, Ohio.

SOME COMMENTS OF OSLER ON CIRRHOSIS

MEDICAL history has preserved for us the opinions of a small group of men who have had an instinctive knowledge of disease processes far in advance of the thought and teachings of their time. Of these men Sir William Osler stands closest to the recent generation; there are few investigators who are not in his debt, and who have not found in his writings an expression of some concept believed to be new. Some of his opinions on cirrhosis of the liver, written in editorial form in the Philadelphia Medical News a half-century ago, are in such accord with modern thought and practice that it seems worth while to call attention to them again after this long lapse of time.

Of ascites, which is still the symptom which first attracts attention to the disease, he has this to say, "The factor which determines the onset of dropsy in cirrhosis of the liver is not always clear. The highest possible grade of portal obstruction, even obliteration of the vena portae may exist without it. . . . . We must look beyond the liver for the explanation of these facts. . . . . The dropsy may be due to a transitory and remediable cause." It is still difficult to give a full and satisfactory explanation of the ascites due to hepatic damage, but it is increasingly clear that the answer is to be sought in a study of the factors which control the passage of fluids across living membranes. Hypoproteinemia and reduced osmotic pressure have recently been shown to be of great importance, and it now seems that there is a rough inverse relation between the latter factor and the rate of transudation. Inert substances, such as acacia, will raise the colloid osmotic pressure of serum and thereby tend to retain fluid within the capillaries; its use in the ascitic stage of cirrhosis is as yet in the experimental stage, but if nothing else is accomplished, studies on this point will afford a means of investigating the significant factors in the pathologic physiology of the formation of transudates.

The membranes involved have still to be studied; it is conceivable, but not altogether likely, that the solution to the problem will be found there. This possibility did not escape Osler's attention; he considered the possibility that, "owing to changes in the serous layer the capillaries are rendered more permeable and without any increase in the blood pressure permit of transudation." That anoxemia, now known to be a fairly constant finding in cirrhosis, may be partially responsible is suggested by the studies of Landis who showed that reduction in the oxygen content of the tissues greatly increased the rate of filtration through frog's mesentery.

Commenting on the prognosis in cirrhosis, Osler was convinced that "the disease may be arrested or even cured" and noted "the personal equation. . . . of the liver tissue" in respect to hepatotoxins. The observations of Bollman on animals with experimental cirrhosis have fully confirmed the possibilities of arrest or cure; he has demonstrated that the pathologic process in the liver can be carried to an almost fatal conclusion; the animals being thereafter restored to normal health and their livers regenerated to a very considerable degree by the use of high carbohydrate diets and glucose given intravenously. Similar clinical results are on record, as Chester Jones has recently shown. Osler feared that, "We probably have not any remedies at our command capable of curing a cirrhotic liver," a point with which all must agree, but it does seem possible to control the symptoms of the disease and induce some degree of repair of the liver itself in certain cases. So far as the variations in the resistance of some animals and individuals to hepatotoxic substances is concerned, this may depend upon dietary habits and the glycogen content of liver tissue; it has been clearly shown that experimental fatty degeneration of the liver requires for its production a diet low in carbohydrate and protein and high in fat and that a high carbohydrate diet will protect the organ against the most severe insults.

Osler's remarks on treatment emphasize some particularly important points; he disapproved of the practice of deferring paracentesis "until diuretics and

CANNED FOODS IN THE CONTROL OF LATENT AVITAMINOSIS B1

● Apparently mild vitamin B1 deficiency in humans is not characterized by very definite or entirely specific symptoms. While such a condition may be attended by anorexia, hypotonicity of the bowel, indigestion, vague pains and malaise, latent avitaminosis B1 hardly presents a picture which is favorable to its early clinical detection. However, there are two procedures which may be employed when this type of avitaminosis is suspected.

The first procedure (1a) depends upon the nature of the response to administration of pure vitamin B1. The second procedure, which has been more widely applied, makes use of the Cowgill formula for calculation of vitamin B1 requirement. By consideration of the actual vitamin B1 intake and the calculated vitamin B1 requirement in any specific instance, the probability of mild avitaminosis B1 may be evaluated (1b).

It is difficult to estimate the frequency of mild vitamin B1 deficiencies in the United States. However, until such information is at hand, it is not illogical to suggest that latent avitaminosis B1 must be regarded as an active possibility in some cases which may come to the attention of the medical practitioner. Fortunately, several factors are operative which give assurance that eventually the incidence of latent avitaminosis B1 will be reduced to a *minimum*.

First, those concerned with human nutrition have today more definite information concerning quantitative human vitamin requirements than ever before in history (2).

Second, every passing year brings marked progress in education of the layman to the necessity of a completely "protective" diet. The control of the latent avitaminoses is, in large part, dependent upon proper food selection and correct formulation of the diet by the layman consumer.

In the establishment of dietary regimes which will be protective against vitamin deficiencies, commercially canned foods may play an important part. Several hundred canned foods are available upon the American market at all seasons of the year. Nutritional research has shown (3) that modern canned foods retain in good degree the vitamin B1 contents of the raw materials from which they were prepared. This great class of foods—available to all consumers regardless of economic status—will contribute substantially to the alleviation and prevention of latent avitaminosis B1 in this country.

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1a. 1935. J. Am. Med. Assn. 105, 1597
b. 1934. The Vitamin B Requirement of Man, G. R. Cowgill, The Yale University Press, New Haven.

2. 1937. J Am. Diet. Assn. 13, 195.

3 1936 J Nutrition 11, 383.
1934. Ibid 8, 449
1932. Ibid. 5, 307.
1932. Ind. Eng. Chem. 24, 457

This is the thirty-second in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.



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cathartics have been thoroughly tried." Purging of patients in this condition is now in general disfavor, and it is equally certain that diuretics have been used to the detriment of many patients. The best practice is now, as it was in Osler's time, to support the liver by all possible means, to correct so far as possible the abnormal composition of the blood, and to do paracentesis as it becomes necessary. In fact, preoccupation with the problem of dropsy as such, rather than attention to the factors responsible for it, is to be blamed for at least some of the difficulties which arise in the course of treatment. Much might be accomplished in the care of the patient if Osler's optimistic view were taken, "The practical point is this, that in certain cases of cirrhosis the effusion results from changes which are not necessarily permanent, and we should not regard the onset of dropsy in every case as the beginning of the end."

Albert M. Snell, Rochester, Minn.

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ACETYLCHOLINE AND THE GENESIS OF PEPTIC ULCER

A NEW chapter in the physiology of the gastro-intestinal tract is being initiated by recent knowledge concerning the chemical mediation of nerve impulses involving the autonomic nervous system. Naturally, some speculation in regard to the effects of these chemical mediators on the normal digestive functions has been aroused and various hypotheses relating to the genesis of pathologic processes are being investigated in the light of these new conceptions.

It is generally agreed that when parasympathetic nerves are stimulated a substance resembling acetylcholine can be recovered from the venous outflow of the stimulated region, and that sympathetic stimulation liberates a chemical substance, sympathin, which is closely related to epinephrine. Acetylcholine has been shown to have an extremely evanescent action and to be destroyed rapidly in the body by a specific enzyme, the choline esterase, which splits the ester into acetic acid and the relatively inactive substance choline. The action of acetylcholine can be prolonged and augmented by introducing drugs such as physostigmine and prostigmin* which inhibit the action of this destructive enzyme; these facts have been applied clinically in the use of acetylcholine or prostigmin, alone or in combination, to increase gastro-intestinal motility (1).

It has also been demonstrated that a substance, the action of which resembles that of acetylcholine, is the chemical mediator of those motor impulses arising in the parasympathetic nervous system which affect the stomach (2) and intestines (3). Sympathetic impulses passing to these regions liberate sympathin which inhibits intestinal contraction (4).

In addition to the known stimulating effect of acetylcholine on the gastro-intestinal musculature the drug usually is regarded as being a specific vasodilator of the peripheral vascular regions. The recent investigations of Necheles and his coworkers (5, 6, 7) indicate, however, that in the arteries of the perfused stomach of the rat and the dog and in the mesenteric and gastric arteries isolated from human beings small amounts of acetylcholine produce vasoconstriction. On the basis of this last observation these investigators concluded that, since the stomachs of patients with ulcer usually exhibit increased motor activity, it is conceivable that a larger or more continuous production of acetylcholine might also occur in these portions. They have assumed that certain parts of the duodenum and the lesser curvature of the stomach are supplied only by end arteries and, therefore, they have considered that a decreased blood flow produced by the action of a hypothetical excess of acetylcholine to these parts of the duodenum and stomach might be a factor in the genesis of ulcer.

There are other clinical and experimental studies which give some support to this assumption. Gastric and duodenal erosions and even ulcers have been produced repeatedly in animals by continuous stimulation of the vagus nerves or by the intraventricular administration of drugs which stimulate the parasympathetic nervous system. That such nerve stimulation, produced by lesions in the human central nervous system might result in the production of fatal ulceration of the stomach or esophagus has been demonstrated by Cushing (8) and others (9). Ulcerations produced in this manner are thought to be the result of hypermotility and hyperacidity, possibly supplemented by accompanying local spasm of the terminal arterioles.

In spite of these observations one must remember that considerable question still exists concerning the occurrence of an increase of free gastric acidity in animals (10) and in man (11) following the administration of acetylcholine. Furthermore, the anatomic studies of Atwood (12) demonstrate that the entire stomach and duodenum are well supplied with numerous arterial branches capable of forming anastomotic channels and that these regions are, therefore, in little danger of localized infarcation due to a decreased blood supply in the end-arteries.

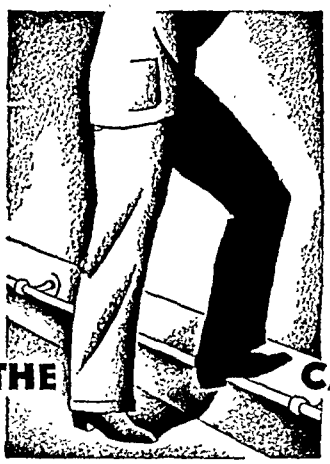
While the possible relationship of the production of acetylcholine to ulcer is being investigated further, it must be remembered that the exact site of the formation, the mode of action and the normal disposition of this substance are still unknown. Likewise, the available evidence is insufficient to explain just what factor or factors control the integrity of the gastro-intestinal mucosa under normal conditions. Whether this control is exercised through maintenance of the proper blood supply or by changes in gastric or duodenal secretion is not known. Until these normal protective mechanisms are more clearly understood, any attempt to explain the probable etiology of ulcer on the basis of some abnormality relating to the chemical mediators of nerve impulses should be held sub judice.

Hugh R. Butt, Rochester, Minn.

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*Mono-hydroxyl-methylammonium methylsulphate.



AMONG THE CAUSES OF HYPERACIDITY

Certain disorders almost invariably, but certain "habits" not much less frequently, are the prolific source of gastric hyperacidity. The "last" drink of liquor, that additional cup of coffee, another pipeful of tobacco, rich food that pleases the palate but displeases the stomach, fear and worry—all must share the blame of mischief-making in the stomach.

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"ABERCROMBIE'S ACUTE ILEITIS AND COMBE-SAUNDERS-CROHN'S TERMINAL OR REGIONAL ILEITIS"—(OR, "CROHN-*GINZBURG-OPPENHEIMER'S* DISEASE")

IT is of interest to the gastro-enterologists, at this time, to be reminded of two very interesting studies and reports made more than a century ago concerning pathologic states of the ILEUM.

John Abercrombie (1780-1844) discussed ACUTE AND SUBACUTE FORMS OF ILEITIS in his book entitled "Pathological and Practical Researches on Diseases of the Stomach, the Intestinal Canal, the Liver, and Other Viscera of the Abdomen," Edinburgh, Waugh and Innes, (Glasgow and London), pp. 238-263, 1828.

At a Session of The College of Physicians in London, held on July 4, 1806, a report by Charles Combe and communicated by William Saunders, Fellow of the Royal College of Physicians, was read on: "A Singular Case of Stricture and Thickening of the ileum"—Medical Transactions, Published by the College of Physicians in London—London, Longman, Hurst, Rees, Orme and Brown, Paternoster-Row, Vol. IV, pp. 16-21, Report III, 1813.

This Report states that the patient, William Payne Georges, Esquire, of a very nervous and delicate habit. Died February 9, 1806. Body opened next day by Combe. The lower part of the ileum as far as the colon was contracted for the space of three feet, to the size of a turkey's quill, etc. An early report (1806) of REGIONAL ILEITIS"!

Included with these brief comments are photostatic reproductions of the original report of this very early (1806) case of REGIONAL ILEITIS or COMBE-SAUNDERS-CROHN'S DISEASE, and the report of Case C11, by Abercrombie (1828).

In Abercrombie's book (Edinburgh, 1828) appears Case C11, page 263, a girl aged 13, about a year before her death, began to be affected with pain of the abdomen and frequent vomiting.

Inspection (lines 22 to 27). "The lower end of the ileum, to the extent of about eighteen inches, was distended, thickened in its coats, externally of a reddish color and internally covered by numerous well-defined ulcers, varying in size from the diameter of a split pea to that of a sixpence. The lungs and all other viscera were healthy."

Hyman I. Goldstein, Camden, N. J.

Abstracts

MEMPHIS DOCTOR DECLARES GREATEST STEP IN ARTIFICIAL INFANT FEEDING WAS CERTIFIED MILK'S INTRODUCTION

DALLAS, October 23—No step in the history of medicine did as much to simplify and make safe the artificial feeding of infants and children as did the production of certified milk, "the most idealistically pure milk the world has ever known," Dr. C. Barton Etter, M.D., a member of the Memphis & Shelby Certified Milk Commission, Memphis, Tenn., declared here today before the Certified Milk Section of the International Association of Milk Dealers convention at the Adolphus Hotel.

Certified milk enables the pediatrician to feed each baby as an individual with individual requirements, Dr. Etter asserted. "We are able to change any integral part of the milk to suit individual needs," he said, "without the necessity of changing the entire structure of the product, and always with the knowledge of the food value of the resultant mixture.

"Such freedom, to those of us who devote a large part of our time to the feeding of infants and children, is invaluable. In no other form of milk now available do we enjoy such freedom. Here we have a milk produced under the most sanitary conditions, hence a clean milk; a milk from tested cows eliminating the possibility of tuberculosis and undulant fever; a milk with the lowest possible bacterial count thus minimizing to the lowest degree the *possibility of intestinal infections*; and, finally, a milk of known chemical constituents standardized the world over, which would allow us to make those modifications necessary to fit the individual case without the necessity of a chemical analysis of the milk to be used.

"Given such a product upon which we can depend so freely, wherever it is produced, we have a basis for a very simplified method of infant feeding. Should an upset result we are familiar enough with our product to be able to recognize the probable cause of the upset and very easily make those changes that should shortly correct it."

Memphis Certified Sales Up

In Memphis, the use of certified milk has increased 20 or 30 gallons daily in the past year, Dr. Etter declared. "If the city of Memphis is to be taken as a fair example," he said, "we must assume that not only do the pedintricians recognize certified milk for its true value but that the public at large is *also recognizing this value*. Certified milk should continue to hold the place which it has so long and so rightfully held at the head of the list of available milks."

ST. LOUIS PHYSICIAN DECLARES CERTIFIED MILK "POTENT FORCE FOR PROGRESS" AT DALLAS MEET

DALLAS, October 23—Calling certified milk a "potent force for progress," Dr. Paul J. Zentay, M.D., Secretary of the St. Louis, Mo., Pure Milk Commission, today told the *Certified Milk Section* of the International Association of



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*Oelgoetz, A. W., Oelgoetz, P. A. and Wittekind, J., Studies in Bowel Drainage, Am. J. Digest. Dis. & Nutrition, 3:549 (October) 1936.

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"Certified milk is a factor that represents a continuous stimulation for a steady advancement in an extremely important phase of public health," Dr. Zentay said. "It leads the way toward the goal of what will be and must be reached sooner or later, i.e., the best possible milk for the largest number of people. Certified milk is small in quantity but like the leaven it acts like a ferment and thereby it is not only capable of unlimited growth but it activates growth unceasingly.

"The health officer necessarily will be interested in a well balanced public health program for his community. An essential part of such a program must be adequate milk control and sanitation. In developing this part of his program the up-to-date health officer may confidently turn to certified as a milk of choice. Why? Because certified has been during its entire existence the standard bearer of the milk industry.

"The milk sanitarian or dairy inspector must be primarily an educator. Where else but on the certified dairy farm can he find a cheerful and willing compliance with the most rigid regulations? For the educator in public health is there anywhere a more concise history of milk sanitation written than in the annually revised editions of 'Methods and Standards' for the production of certified milk?

"The physician must consider certified milk his first choice because he will demand that the cleanest and most nutritious milk should be available for his patients. Certified milk has always been the very own product of the medical profession, and has been a unique contribution of American medicine to the rest of the world of which it may be justly proud. The reason for the pediatrician's choice of certified is in the invaluable combination of original cleanliness and sanitation with scientific nutritional enhancement of food values.

"Is it not high time for us to educate mothers that in case of milk you inevitably will get only what you pay for? Every mother should be told that the higher price of certified milk is paid for superior value in every quality of milk."

New Orleans Physician Declares Babies Fed Certified Milk Have Greater Freedom From Disease

DALLAS, October 23 — Infants and children fed certified milk have more resistance to infections and greater freedom from disease, Dr. Roy E. de la Houssaye, M.D., President of the New Orleans, La., Pure Milk Society, asserted here today before the Certified Milk Section of the International Association of Milk Dealers convention at the Adolphus Hotel.

"The diet of the infant and child largely determines his well being," Dr. de la Houssaye said. "I have used *almost every kind of milk in my* practice. My observations lead me to say certified milk-fed infants and children have more resistance to infections and greater freedom from disease. I have noticed that infants and children fed on other than certified milk need three or four times the accepted dose of cod liver oil.

"What is certified milk? I must go back about 40 years. Statistics show there were 300 deaths, before the completion of the first year, to every 1,000 children born. Infants and children hardly had a chance. When you saw one sick with diarrhea, it nearly always meant death. What single factor did most to change this situation?

"Dr. Henry Coit of Newark, N. J., lost a child and, through the tragedy in his own home, realized this terrible condition. He found a dairyman who was willing to produce milk according to the rules Coit made at that time. Babies and children using this milk did much better than others. The rules and regulations were added to; more dairies wanted to produce this kind of milk; the same rules were adopted in other cities; this progress continued—hence the birth of certified milk.

"Certified milk is the purest form of raw milk obtainable. It is produced in accordance with the regulations prescribed by the American Association of Medical Milk Commissions. You must know that the men in the dairy industry who conform to these high standards are leaders. They are forever trying to raise the standards. They employ trained technical men whose business it is to see that better milk is produced. This necessarily induces careful feeding of the certified dairy herd.

"In working for better milk, which is—and always will be—certified milk, I am sure everyone knows that we receive, *as our only* compensation, healthier infants and children.

Human Nutrition Linked Closely to Diet of Cow, Dairy Bureau Man Says

DALLAS, October 22 — Improvement of human nutrition is linked closely to the diet of the cow, since there is much evidence of the value of milk as a supplementary or protective food and since in all known respects in which milk is particularly valuable its nutritive value is affected by the quality of the ration fed to the cow.

C. A. Cary, Acting Chief of the Division of Nutrition and Physiology of the Bureau of Dairy Industry of the United States Department of Agriculture, Washington, D. C., made this statement today in a paper read before the Certified Milk Section of the International Association of Milk Dealers convention at the Adolphus Hotel here. The paper was read by Dr. O. E. Reed, Chief of the Bureau of Dairy Industry, *in the absence of Mr. Cary.*

"Numerous nutritional surveys indicate that the dietaries of children and adolescents, and even of adults, may frequently be deficient in some respect," Mr. Cary wrote. "The more intimate our knowledge of the etiology of disease, the more evidence there seems to be that many human ills may be associated either directly or indirectly with such dietary deficiencies. And, as additional nutritive factors are found to be essential in the human diet, the evidence of the value of milk as a supplementary or protective food increases.

"The diet of a cow does decidedly affect the nutritive value of her milk in a number of important respects. The recent work at Wisconsin on the nutritive value of milk from cows on pasture and on winter rations indicates that we do not know all of the dietary essentials that are thus affected.

"As a supplementary food, milk is most highly esteemed as (1) a rich source of protein of high biological value, (2) as a source of vitamin A, (3) as a source of vitamin B, (or riboflavine), and (4) as a source of calcium and phosphorus in a form, or as a dietary combination, that renders these inorganic constituents readily assimilable. In all of these known respects in which milk is particularly valuable, its nutritive value is affected by the diet of the cow."

Dallas Physician Speaks Before Certified Section of Milk Meet; Urges Milk Use Throughout Life

DALLAS, October 23—Nutritional requirements from the cradle to ripe old age are met by certified milk, Dr. John G. Young, M.D., Chairman of the Dallas County Medical Milk Commission, declared here today before the Certified Milk Section of the International Association of Milk Dealers convention at the Adolphus Hotel. His subject was "The opinion was one prevalent, Diet."

"Throughout life, the diet requires the vital food, milk," Dr. Young said. "When milk is so essential, we should use and prescribe the best product obtainable. Certified milk, being the best obtainable, meets the requirements.

"The place of certified milk in the diet has been established and proved. Nothing is done to pure, clean milk, properly produced from well fed cows. It is protected from harm and given to the consumer in a state ready for the

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best possible results we know milk can give. The nutritional requirements met by milk are met by certified milk from the cradle to ripe old age."

Dr. Young is an instructor in pediatrics at Baylor Medical School; attending pediatrician at Baylor Hospital and at Methodist Hospital; Chief of Staff of the Freeman Memorial Clinic; Fellow of the American Academy of Pediatrics; President of the Texas Pediatric Society; and President of the Dallas Pediatric Society.

"The growing child needs milk," Dr. Young continued. "It is possible to exist without it but not in a state of optimal nutrition, good health and well-being. As a pediatrician I realize this and so do most pediatricians. And as life through to old age is continual change, with repair, regrowth and modification occurring in the body, there is needed this vital food, milk, for the same 'sense of well being,' optimal nutrition and health.

"Those interested in certified milk still agree that mothers milk is the milk of first choice when available in quantities sufficient. When this supply is not provided, some other suitable food must be supplied. For ages, and through much research and clinical observation, this other suitable source has been found to be milk. With this there is no good argument.

"If milk, then the best milk, and so certified milk is the choice. A precious gift for a precious person. No other milk is 'just as good as certified milk.'"

UNPASTEURIZED MILK, CONSUMED BY MORE THAN HALF OF U. S., CAUSED 42 EPIDEMICS IN 1936, SCIENTIST SAYS

DALLAS, October 22—More than one-half of the 123,000,000 people in the United States are still consuming potentially dangerous raw, or unpasteurized, market milk even though the public health importance of milk pasteurization has long been established, Dr. James A. Tobey, prominent New York scientist and health expert, told the annual convention of the International Association of Milk Dealers here today.

Only about 47 per cent of the fluid milk produced in this country is pasteurized, it was declared by Dr. Tobey, until recently Director of Health Service of The Borden Company. The risk of epidemics due to contaminated raw milks of low grades is still very great, he asserted.

"In 1936 there were 42 epidemics of milk-borne diseases in the United States, involving 1547 cases of preventable diseases, and 28 unnecessary deaths, as reported by the United States Public Health Service," he said. "In every instance these unfortunate outbreaks of typhoid fever, septic sore throat, scarlet fever, and other communicable diseases were caused by infected raw milk of low grades. The only gratifying feature about these epidemics is the fact that the number is less than the country's average for the past ten years, indicating a gradual improvement in the small town and rural milk supplies in which most of these outbreaks occur.

Texas Cities Slow to Pasteurize

"In 1923 only about 70 per cent of the market milk in Dallas and Fort Worth was pasturized, and in 1931 only 80 per cent was accorded this important safeguard. Except for Galveston, where 80 per cent of the supply was pasteurized in 1931, other Texas cities have been unfortunately reticent in adopting this sensible safety measure, which ought to be universally applied for the best interests of the common health."

Dr. Tobey gave an analysis of statistics of pasteurization by sections of the country and by cities. Pasteurization has been much more widely adopted in the East North Central, Middle Atlantic and New England States than in the South Atlantic and South Central States, he declared, while the Pacific and Mountain States occupy a position between these other sections. While the southern states

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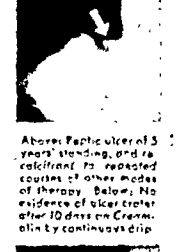
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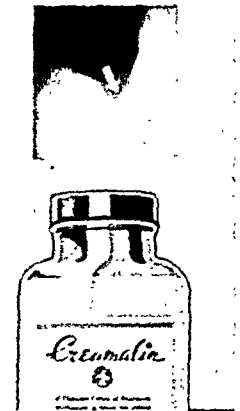
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A RARE CASE OF PRIMARY LIVER CARCINOMA IN LIVER FLUKE DISEASE (CLONORCHIS SINENSIS) - - - - - - - - - - - - - - - - - - *William A. Swalm, M.D., Edwin S. Gault, M.D. and Lester Morrison, M.D.*

EVOLUTIONARY CONTRIBUTIONS TO THE GENERAL FUNCTION OF THE GALL BLADDER - *Frank Gorham, M.S. and A. C. Ivy, Ph.D., M.D.*

THE MECHANISM OF PRODUCTION OF DIGESTIVE SYMPTOMS ASSOCIATED WITH UROLOGIC PATHOLOGY - - - - - - - - - - - - - - - - - - *P. B. Welch, M.D., Milton M. Coplan, M.D. and Roy J. Holmes, M.D.*

THE EFFECT OF BLEEDING ULCERS AND HEMORRHAGIC ANEMIA UPON WHOLE BLOOD COPPER AND IRON - *Adolph Sachs, M.D.*

ACQUIRED HEMOLYTIC JAUNDICE - - - - - - - - - - *J. W. Rastetter, M.D. and Francis D. Murphy, M.D.*

STUDIES ON THE CONTROL OF GASTRIC SECRETION - - - - *A. J. Atkinson, M.S., M.D. and A. C. Ivy, Ph.D., M.D.*

INFLUENCING FACTORS IN NUTRITIONAL DEFICIENCY DISEASE - - - - - - - - - - - - *Russell L. Haden*

CLINICAL AND PATHOLOGICAL MANIFESTATIONS OF CARCINOMA OF THE STOMACH - *Abel Levitt, M.D., F.A.C.P. and John F. Argue, M.D.*

THE VALUE OF DIAGNOSTIC NON-SURGICAL BILIARY DRAINAGE AS COMPARED WITH CHOLECYSTOGRAPHY (AN ANALYSIS OF BILIARY DRAINAGE FINDINGS IN 64 OPERATED CASES COMPARED WITH FINDINGS BY CHOLECYSTOGRAPHY IN 60 OF THESE CASES) - - - - - *William T. Doran, M.D., John Wilfrid Forster, M.D. and Lester C. B. Spier, M.D.*

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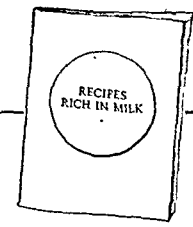
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have recorded gratifying increases in the amount of milk pasteurized, the greatest percentage of urban sales of the hazardous raw milk is still in the southern and southwestern cities, he said.

"The percentage of milk pasteurized in American cities of 10,000 or more population increased from 81.8 per cent in 1927 to 87.5 per cent in 1931," the speaker continued. "There are in this population group something over 700 cities having a total population of more than 58,000,000 persons, according to the 1930 federal census.

"As the population of various communities decrease, however, the proportion of pasteurized milk also decreases, until in the rural sections it is close to zero. Thus, a recent survey by a committee of the International Association of Milk Sanitarians reveals that an average of only 38.6 per cent of the milk in communities of 1,000 to 10,000 population is now pasteurized. In this population group, there are more than 15,000,000 people, as shown by the census of 1930.

50,000,000 Live Where No Pasteurization

"Another 50,000,000 persons in the United States reside in villages having less than 1,000 population and in rural sections of the country, where pasteurization of milk, at least for human consumption, is seldom, if ever, practiced.

"The data in the Public Health Service report for 1931 shows that in this year there were only 35 American cities in which the entire milk supply was reported as pasteurized. There were, however, another 64 cities in which all milk except certified, the highest grade of milk and the only legitimate exception to the goal of universal pasteurization, was required to be pasteurized.

"Of the 99 municipalities on this honor roll, 16 were in Illinois, where incidentally 80 per cent of the state's milk supply is said now to be pasteurized. Thirteen of the honor cities were in Ohio, and there were 11 each in Massachusetts, New Jersey, and New York, these four states with Illinois accounting for two-thirds of the communities having from 99 to 100 per cent pasteurization."

Dr. Tobey declared that a current survey of the status of pasteurization, now being undertaken by officials of the United States Public Health Service, may divulge further improvements over the figures cited but, even so, the record is unquestionably not as creditable in many parts of the country as it should be. Pasteurization has made noteworthy progress, he asserted, and is making splendid advances, but there is still much to be accomplished.

Universal Pasteurization Can Be Achieved

"The goal of universal pasteurization in this country can be achieved by the cooperative and zealous efforts of competent health officials, comprehending physicians, a perceptive dairy industry, and an enlightened public, educated to demand the quality in its milk supplies that all progressive milk dealers are more than willing to give," the speaker continued.

"Although the organized medical profession, as represented by the American Medical Association, strongly advocates pasteurization, many individual physicians do not seem to realize the significance of this necessary process. In some parts of the country, education of the professional man in this respect is as much needed as is education of the presumably more ignorant layman.

"The Place of Certified Milk in the and is not yet wholly dispelled, that pasteurization is merely a corrective for an impure milk supply. Today that idea is a delusion, for pasteurization is

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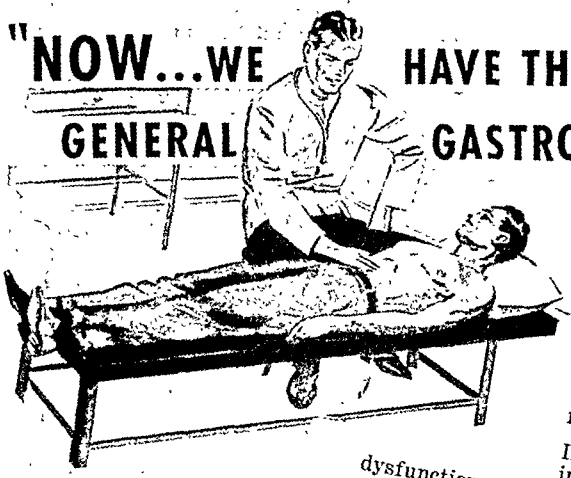
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Disturbance of the Cardiovascular System in Nutritional Deficiency. J. A. M. A., Vol. 109, pp. 786-793, Sept. 7, 1937.

Disease of the cardiovascular system is usually studied from the standpoint of infections and degenerative processes. Since it is the most important cause of death, the study of the relationship of nutritional deficiency to it is important. Severe dietary restrictions result in bradycardia, hypotension, and a decreased metabolism. The rate of blood flow is also considered to be decreased in these cases. If prolonged, fatty degeneration of the myocardium may result. It has been observed that cardiac standstill occurs more frequently in malnourished dogs and cats when operated upon, than in well nourished ones. It has also been observed during famines that malnourished patients are poor surgical risks.

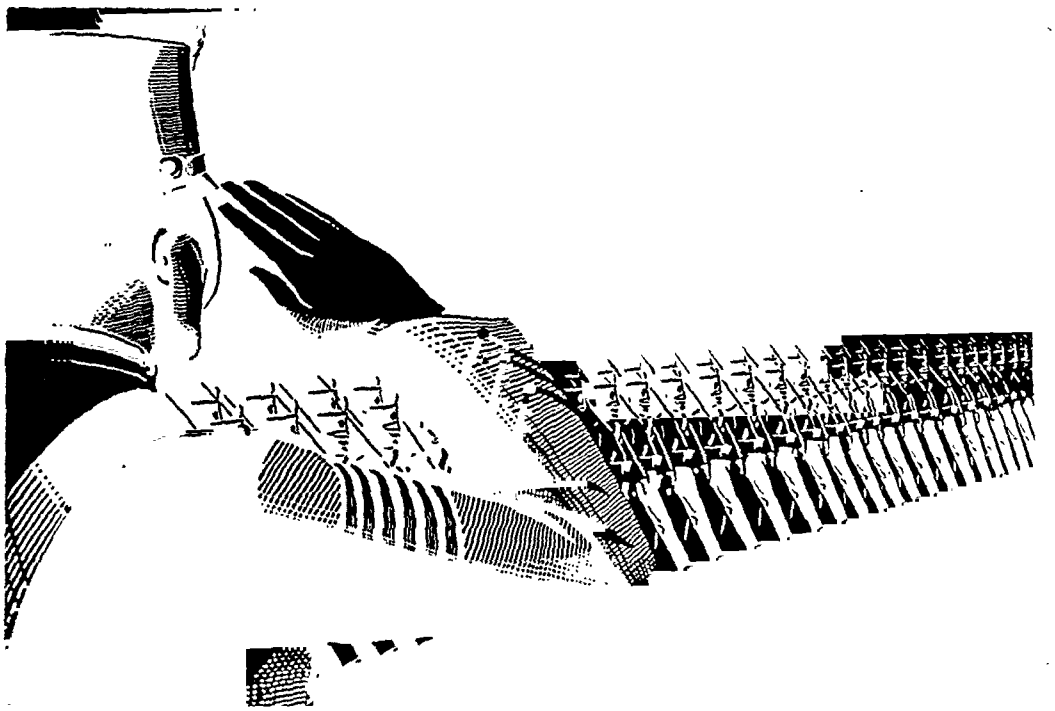
A deficiency of protein results in nutritional edema, a lowering of the serum protein, and in the presence of heart disease the tendency for exudation into the pleural, pericardial, and peritoneal spaces and of pulmonary edema is increased.

Reduction of the blood sugar results in symptoms of hypoglycemia as occur in hyperinsulinism and diabetes with insulin shock.

Dehydration as occurs in diarrheal conditions, fevers, fistulae (biliary, etc.), prolonged vomiting, duodenal drainage, results in circulatory collapse and shock of dehydration. This is due to a reduction of blood volume, hemoconcentration and the accumulation of toxic waste products in the body.

Hypochromic or macrocytic anemias produce an increase in the cardiac output and velocity of blood flow, a hypotension and an increased pulse pressure. In pernicious anemia, fatty degeneration of the myocardium occurs producing the "tiger lily" appearance typical of far advanced stages of this disease. X-ray also shows some cardiac enlargement and physically there may be systolic and rarely diastolic murmurs heard.

Vitamin deficiency results first in biochemical changes, later functional



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and finally structural. In the early stages, this may be a reversible process, but as time goes on these changes may proceed to a state of nonreversibility. Deficiency of vitamin B results in beriberi, which in its "dry" form is characterized by muscle wasting, and peripheral neuritis, while in its wet form, by cardiovascular disturbances and generalized edema. The cardiovascular symptoms of beriberi are dyspnoea on exertion, palpitation, tachycardia, embryocardia, gallop rhythm, prominent cardiac and epigastric pulsations and bounding peripheral pulses. The heart may be normal in size or enlarged, and systolic, rarely diastolic murmurs may be present. Cardiac asthma may occur. The arterial pressure is normal or the systolic may be moderately increased. Edema may be present. The electrocardiogram usually shows alteration in the T waves. Pathologically, there is no constant gross finding except slight dilatation of the right ventricle, but histologically, there is a degeneration of the myocardial fibers, swollen collagen, perivascular "edema," and separation of the myocardial bundles. It has also been noticed that infantile beriberi of the Orient occurs in breast fed babies. This may account for some of our cases of "idiopathic" cardiac hypertrophy.

Experimental evidence indicates that a deficiency of vitamin C predisposes to cardiac lesions. Once these occur, however, it does not cure them. Cardiac changes that occur in vitamin D deficiency can be ascribed to the simultaneous presence of vitamin B_1 deficiency.

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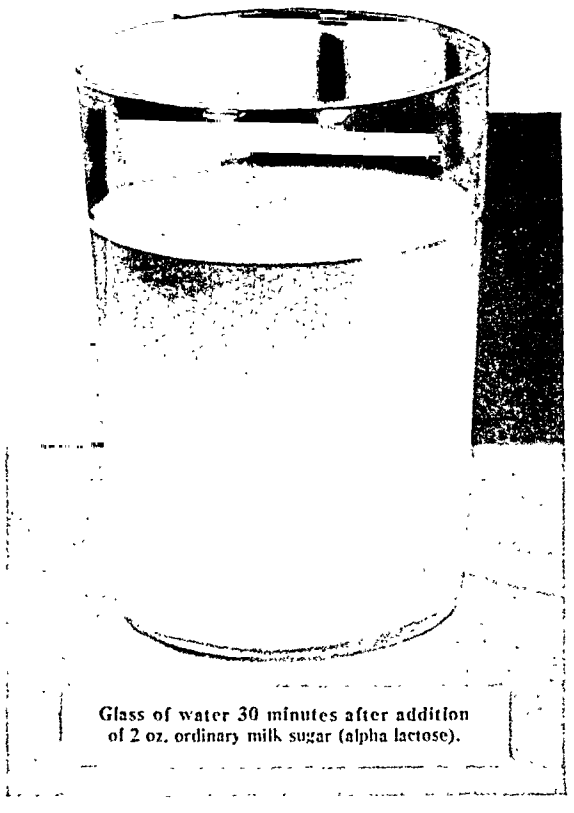
Congenital Adhesions of the Gall Bladder. Ann. Int. Med., XI, 379, Aug., 1937.

The material upon which this paper is based came from the Department of Anatomy of the Boston School of Medicine and Surgical Clinic of the Massachusetts Memorial Hospital and was an article contributed to an Anniversary volume in honor of Dr. Joseph Hersey Pratt.

The author states that abnormal peritoneal attachments to the gall bladder are more common than are inflammatory attachments. He calls attention to the nature of the sheets of tissue that run from the lesser omentum to the gall bladder, to the duodenum and the colon as being simple folds of peritoneum, with definite relation, definite structure and regular vessel arrangement. These, therefore, are concluded to be no evidence of past infection of a gall bladder. The author thinks that inflammation as a result of infection has been emphasized too greatly in pathological conditions of the gall bladder to the neglect of anatomical and metabolic factors. He thinks that cholesterosis is no more a manifestation of infection than is atherosclerosis in blood vessels. He looks upon both as evidences of degenerative changes as the result of toxic and metabolic disturbances rather than from inflammatory causes.

He offers two methods of determining whether or not a peritoneal attachment is a congenital one or an inflammatory one. The development of abnormal peritoneal attachments to the gall bladder are rather simple from an embryological viewpoint, the primary digestive tube having an anterior and a posterior mesentery and in the rotation of the stomach the posterior mesentery becomes the greater omentum, while the anterior becomes the lesser. From the anterior mesentery a bud grows out to form the liver, bile ducts and gall bladder. Usually the anterior mesentery is stopped at the common bile duct and portal vessel, but it occasionally becomes more extensive and runs from the common duct over to the gall bladder, down the duodenum and to the hepatic flexure of the colon, even as far as the right lobe of the liver and may, he thinks, close the foramen of Winslow. This bit of anterior mesentery may become a mere slight band of tissue running along the lesser omentum to the cystic duct or it

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may be an extensive sheet of tissue. It may develop a mesentery and the gall bladder become enfolded, supported in these tissues. Sometimes it passes over the gall bladder without attachment to it. In some cases the tissue may be absent both above and below, leaving the band from the lesser omentum across the duodenum to the anterior surface of the gall bladder only.

The author emphasizes that in all these types general relations are the same except that different parts of the sheet tissue are missing. The opinion is expressed that such terms as "periduodenitis" and "peritholetystis" or "essential periduodenitis" only contribute to the general misunderstanding and false operative diagnoses.

A resume of the literature by Meyers and Bloom is quoted, in which those authors found 20 per cent of abnormal peritoneal attachments of the gall bladder and duodenum to be in apparently normal individuals. In their own assessment 54 per cent were found to be congenital membranes and only 5 per cent showed inflammatory adhesions. In the authors' material 51 subjects were studied and abnormal peritoneal attachments to the gall bladder were found in 45 per cent. The gall bladder in every one of these cases appeared to be normal. In a series of 100 patients in which a cholecystectomy was done by the author 18 per cent showed definite abnormal peritoneal attachments to the gall bladder.

The question is raised as to whether these congenital peritoneal attachments to the gall bladder, duodenum and colon may produce definite symptoms. The author thinks that perhaps the bare suggestion of the symptoms produced in this connection, such as vague discomfort in the right upper quadrant, loss of appetite, a sense of bloating, nausea, sour stomach, may be helpful indications of anatomical abnormalities which prevent a normal function. Abnormalities of duodenal outline are frequently shown in X-ray studies. The constancy of deformity of the duodenal bulb in ulcer as contrasted with shifting deformity of Duval is stressed. Duval's deformity is differentiated from an irritable cap by the fact that in the former the cap is filled but the deformity occupies a varying segment and remains as irregular atrophy. Constriction of the gall bladder or of its ducts by these abnormal sheets of peritoneal tissue running across the duodenum may result in discomfort and irregular pain in the right upper quadrant, even with nausea and vomiting. These symptoms are relieved by the removal of these congenital adhesions, usually with cholecystectomy. Since relief follows such operative procedures in cases where the gall bladder was restricted in its mobility by these congenital adhesions would seem to argue that the adhesions were the cause of the trouble.

The author concludes in his summary that congenital peritoneal adhesions to the gall bladder are much more common than ordinarily realized, being found in about one-fourth of the population, that while some of these adhesions may not produce symptoms some of them do. The symptomatology is not clear and is rather designated by the term *vague*. These patients are often neurotic. Preoperative diagnosis treatment consists of medical care with a view of relief to the alimentary lodes, psychological care and finally surgery for those cases where definite abnormalities obtain and where other measures have failed. The operative treatment consists usually in the removal of the gall bladder and the section of band or sheath of peritoneal tissue. It is urged that care be taken to prevent secondary adhesions, but no suggestions are offered as to how these be prevented.

Virgil E. Simpson, Louisville.

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HURST, SIR ARTHUR.

Melanosis Coli. Guy's Hospital Reports, 87:332-342, July, 1937.

The author discusses melanosis coli from the historical standpoint, the nature of the pigment, morbid anatomy, histological appearances, and etiological relationship of carcinoma, constipation, purgatives and diarrhea.

Two cases are presented in which the melanosis coli cleared up while the patients were under observation.

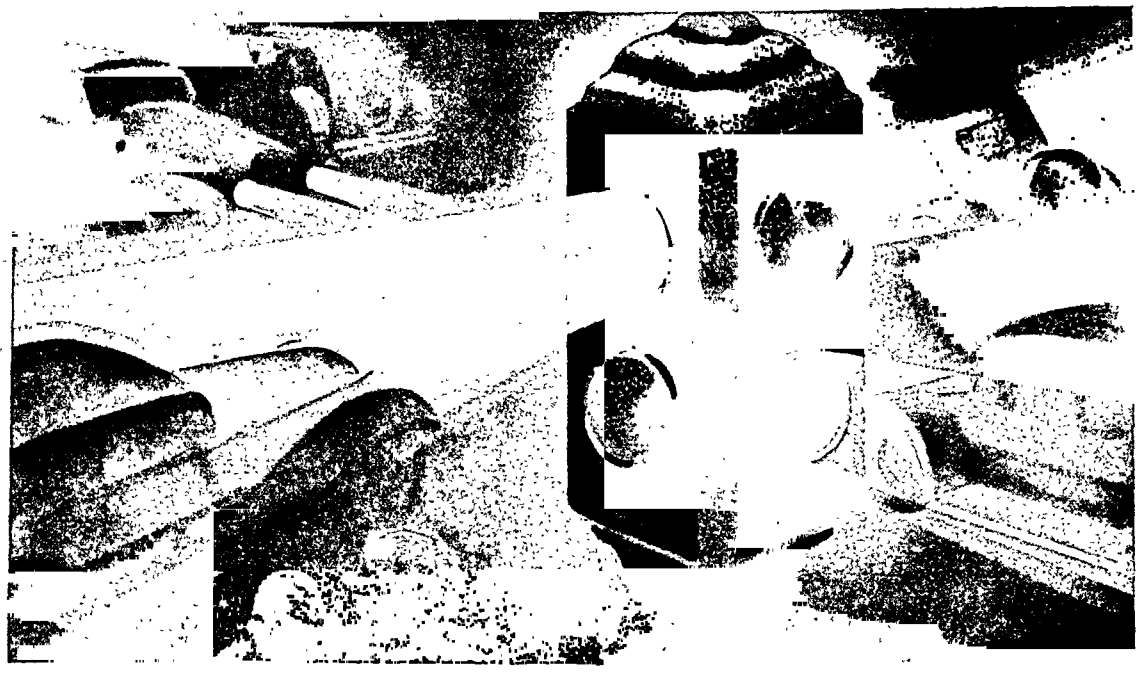
The following conclusions are presented from a review of the literature and a study of the author's own cases:

Some degree of melanosis coli was present in 11.2% of an unselected series of cases autopsied. The incidence is higher above the age of forty (17.7%), and still higher in carcinoma of the colon (50%), the melanosis in the latter being more intense above than below the growth. Melanosis coli is due to the deposition of a melanin-like pigment within large mononuclear cells in the mucous membrane of the large intestine and appendix. The chief causative factor is said to be artificial diarrhea produced by aperients which results in excessive putrefaction of proteins throughout the colon. The aromatic protein disintegration products are absorbed by the mucous membrane of the colon and converted into melanin by the action of a tyrosinase-like ferment. The pigmentation of the colon disappears with cessation of the diarrhea under treatment. Melanosis occurs four times as frequently in persons with carcinoma of the colon as in those without. It is usually confined to the part of the colon proximal to a carcinomatous obstruction in which stasis of semi-fluid faeces leads to excessive putrefaction and the production of precursors of melanin.

Hanes M. Fowler, Fort Wayne.

MISSISSIPPI VALLEY MEDICAL SOCIETY AWARD

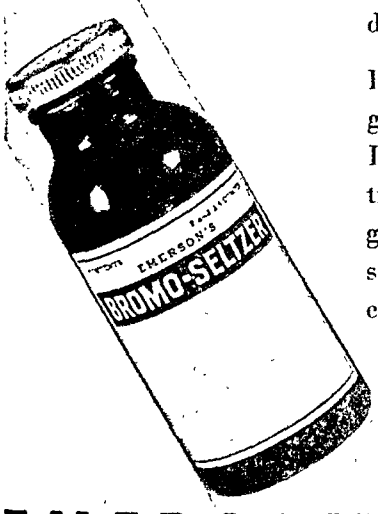
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CONNOTATIONS. H. J. Sims, Denver, Colo.

Bone pathology dates to the time of Kolliker, who in 1873, propounded his osteoblastic and osteoclastic theory of bone production and bone absorption.

In 1835, Glenard published his thesis on visceroptosis. In addition to his description of the etiology, pathology and symptoms, he made the statement that "these subjects were unfortunate in that there was no treatment that had ever been devised which had done them any good and that," in his opinion, "they were consigned to a life of invalidism."

Meaker, in 1923, indisputably demonstrated tubal spasm actually existed.

Maisonneuve, in 1853, described gas gangrene under the name of gangrene foudroyante. In 1864, Pirogoff described the condition as acute gangrenous edema. Pasteur later described the causative organism as the vibrion septique.

Lister was almost deaf and blind during his last three years of life.

Errors are frequently the stepping stones to suffering humanity. Spencer Wells operated for an ovarian cyst and found a tuberculous abscess. He unknowingly established the surgical treatment for peritoneal tuberculosis. He, likewise, supposed an uterine fibroid was the cause of jaundice in an eighteen year-old girl. The spleen, and not a fibroid, was removed. Thus—inaugurating the surgical treatment of hemolytic jaundice.

Runge, in 1834, discovered carbolic acid. Its use was restricted to cleansing the sewage of the town.

In 1863, Jules Lemaire, a French pharmacist, wrote a book on carbolic acid and recommended its use for dressing wounds.

Von Bergmann, in 1886, was the first to use steam sterilization for instruments and dressings.

Partridge, in 1862, an English surgeon of great distinction, was called to Italy to locate a bullet in the ankle of Garibaldi. Not satisfied with his opinion, Nelaton from Paris was consulted. He made a steel probe with a porcelain tip. A metalic stain on the porcelain tip resulted when brought in contact with lead. As a result, he located and removed the bullet.

Joseph Jackson Lister, the association with Thomas Hodgkin, in 1827, determined the diameter of the red corpuscles and their rovleaux-formation.

Henry Gray, author of "Gray's Anatomy," did not live to see its publication. He died of small-pox at the early age of thirty-two.

Lister, in 1867, performed his first breast amputation on his sister.

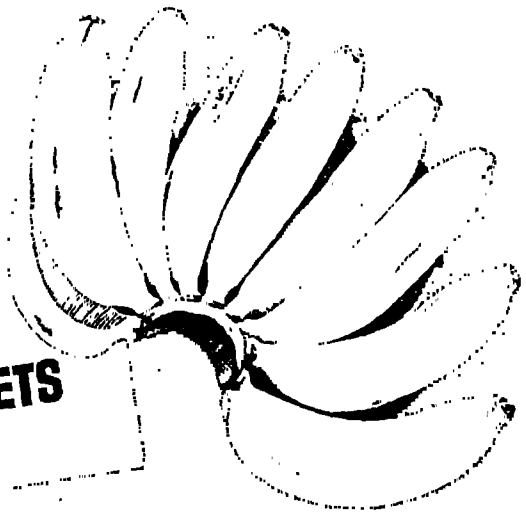
VOLINI, I. F., WIDENBORN, H. L. AND FINDLAYSON, B.
Experimental Duodenal Ulcer. S. G. O., Vol. 65, No. 2, pp. 159-163, Aug., 1937.

In a series of 45 dog experiments in which the author successfully produced intestinal ulceration by the Exalto and Mann Williamson methods, the mucosa of the duodenum showed ulceration in 28 instances. The ulcers varied in size, depth and number. It seemed that the longer the animal survived after operation the smaller and less numerous the ulcers were. The cause of these ulcers is not clear; neither trauma nor interference with blood supply are likely causes, nor is food trauma a possible factor here. While the reaction of bile is frequently acid rather than alkaline it does not seem probable that it would be great enough to produce ulceration in the isolated duodenal loop.

The author reports these observations because no reference to such ulceration in the isolated duodenum has been seen by him, and in the hope that further study and research may be stimulated by this report.

N. M. Percy, Chicago.

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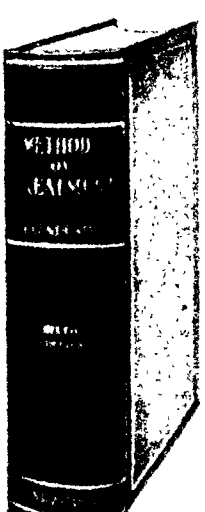
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The Dietary Problem of the Food Sensitive Patient

By

ALBERT H. ROWE, M.S., M.D.

SAN FRANCISCO, CALIFORNIA

IT is generally recognized that food allergy may affect practically any structure of the body and thereby produce mild to severe, acute, or chronic manifestations arising especially in the naso-bronchial, cutaneous, gastro-intestinal, uro-genital, and nervous tissues. Because of this, physicians are increasingly eliminating many foods from the diet either because of positive skin reactions, or because of the patient's history of possible idiosyncrasies. Too often such foods are eliminated, purely because of positive skin reactions, without the realization that many positive reactions to foods are non-specific, and that allergy frequently exists to foods not indicated by skin reactions. This has made the use of "elimination diets," modified, if desired, by positive skin reactions, of definite value in the diagnosis and control of food allergy. In the use of "elimination diets" emphasis must be given to the absolute necessity of providing the patient with menus, recipes, and instructions which will assure the possibility of adequate and reasonable meals obtainable at home or in restaurants or hotels—meals that meet caloric and metabolic requirements.

Thus the physician must assume the responsibility of placing the patient suffering with probable food allergy, on satisfying and appetizing meals from foods which are not productive of evident sensitization. Undesirable weight loss, protein, vitamin, and mineral deficiencies must not occur, especially because of the necessity of keeping patients on "elimination diets" often for prolonged periods of time if tissue changes from chronic allergic reactivity are to be finally eradicated. Patients must not be given a mere list of foods without explicit directions about menus which can be prepared in and away from home. The necessity for such menus has always been stressed in the use of my "elimination diets." In my work, moreover, many recipes have been developed for wheat, milk, egg, and cereal-free bakery products, desserts, and candies. Menus for restaurant, hotel, and home diets are published and should be made available to patients on "elimination diets" or other trial diets. The comparative frequency with which patients are sensitive to one or even to all cereals has emphasized the importance of a cereal, milk, and egg-free elimination diet, which is now the routine Elimination Diet III. For this diet, potato, lima bean, and soy bean flour have been used very successfully.

The ability to make such bread, cake, cookies, candy, or dessert requires care in following the published recipes, and varies with the personal skill and persistence of the cook or the baker. Many patients have excellent results from their efforts. The failure of others with the same recipes is at times difficult to explain.

Because of the time and care necessary to make these products without wheat, milk, or eggs, or any cereals, I have, for many years, enlisted the cooperation of local bakers. One, especially has been successful and is now distributing to patients according to their dietary requirements the following wheat, milk, and egg-free products, many of which are prepared fresh every day:

lima potato bread	corn and rice muffins
soy lima bread	corn muffins
rice bread	rye muffins
rye bread	soy lima snails
lima cookies	soy lima apricot cupcakes
lima molasses cookies	soy Danish snails (frosted)
corn and rice cookies	soy lima toast
rye cookies	cocoanut lima molasses squares
lima potato cup cakes	rye coffee cake
lima sugar cookies	lima soy cake
rice sugar cookies	fruit squares—lima crust
soy bean doughnuts	soy lima pineapple upside down cake
apricot pies—lima crust	
soy lima muffins	

Obviously some of these bakery products, as made by professional bakers, are difficult to reproduce in the ordinary kitchen, since their quality depends so much on special technique, and particularly on the ovens used in commercial work. Similar products will necesarily have to become available in most large cities throughout the world, so that the demands of the multitude of sufferers from food sensitizations can be met. It will also be desirable for certain national food companies to develop wheat, milk, egg, and cereal-free products, breads, probably in a sliced and toasted form, cookies, etc., which can be dispensed in air-tight packages to ensure fresh lasting qualities. It will be necessary that every ingredient of such products be printed on the package, a procedure that should also be enforced on all other food products sold to the public.

With such local and national distribution of products of varying composition, sufferers from food allergy, and physicians who are supervising their problems will be greatly aided in the satisfactory control of symptoms. As people become more aware of the frequency of symptoms arising from food sensitizations, hotels and restaurants will also necessarily take cognizance of the fact that all food is not tolerated by all individuals, and bakery products of varying content will be more generally available; and accurate information about the actual content of various foods on the menus will be more easily and cheerfully obtainable than it is today.

More definite discussion needs to be given to individual foods and allergens which cause sensitization. Milk allergy, especially, offers many difficulties. As stressed by Ratner (5) especially, evaporated milk is

denaturized to such an extent that some milk-sensitive infants can tolerate it without symptoms. In older children and adults, I have not found the use of such milk so successful in the control of symptoms due to milk allergy, and the complete elimination of all milk, usually with the exclusion of butter and other milk products, has been necessary for the eradication of symptoms. When sensitization exists to only the lactalbumin of cow's milk, fresh of preferably canned goat's milk, as prepared by the Myenberg Company of California, may be tried.

In infancy, a soy bean product like Sobee, can take the place of milk, and, as Clarke recently suggested, is taken more avidly by the infant if it is mixed with banana milk, either prepared from the banana flour or from the fresh fruit. If allergy to the bean or the banana exists, then almond milk prepared according to my former directions (1) may be used. Recently canned, homogenized beef or lamb has become available as excellent protein substitutes for milk. Such preparations can be diluted and served as a drink, in a bottle, or as a soup. Beef, and certain vegetables, minerals, and vitamins have been combined in a homogenized preparation called Cemac which can also be used in milk-sensitive patients. The use of pure beef or lamb, however, with the additional use of selected pureed or strained vegetables, minerals, and vitamins according to the patients demands, and evident or possible allergies thereto, would seem preferable.

When milk is excluded from the diet of older children and adults, other proteins such as meat or eggs to which sensitization does not exist, must be given in sufficient amounts to meet protein requirements. Homogenized beef and lamb and other meats will probably be of use in certain cases. Protein need may also be met in part by an extra intake of legumes, providing sensitization to them does not exist. When the use of butter must be forbidden, peanut, almond, or soy bean butters may be used, care being taken that an oil is not added in their manufacture which might give rise to allergy. When cottonseed allergy is not present, a butter substitute may be prepared from well-chilled Crisco, salted to taste. Such a product is now available on the market. A similar product could well be prepared from coconut oil or butter. A noncaloric butter substitute, made from a solid petroleum base, artificially colored. salted to taste, and flavored with a trace of butyric acid is also sold.

It is also helpful to advise the free use of jams and jellies made from fruits in the prescribed diet as a substitute for butter on bread, and chicken fat or bacon grease are at times also acceptable. In the patient who is markedly allergic to milk, as with all other foods to which definite sensitization exists, it is most important to stress over and over again the absolute necessity of eliminating every food product from the diet which contains a trace of milk or any of its products. Too often it is not realized that ordinary bread, cookies, and foods such as Ovaltine contain varying amounts of milk.

The difficulty in preparing a menu and nourishing infants or children without eggs is much less than without milk. Egg allergy, however, is extremely common, especially in children, and seems to be the initial allergy which gradually leads to the development of many others in certain cases. At times patients can tolerate the eggs of one bird and not of another, though usually allergy exists to several different eggs, probably due to proteins common to them. Such occurrence has been demonstrated experimentally. Occasionally patients may be allergic to the egg, meat, and even to feathers of chickens, probably due to the presence of a common allergen in them all.

A few patients are sensitive to several meats. Allergy to pork is probably most common, that to beef and to lamb occurring with decreasing frequency. Skin reactions may or may not occur to such proteins. An occasional patient, as in the case with chicken allergens, is allergic to milk, beef, and cattle hair in varying degrees. It must be appreciated that prepared meat products such as sausage, bologna, and frankfurters contain different kinds of meat, cereals, at times egg, and various spices, which make them entirely unsuitable for inclusion in an elimination diet, especially during the diagnostic period.

For several years, recognition of yeast allergy has made necessary the use of yeast-free baking products in sensitized patients. Such patients are also affected by the yeast used in beer, and the fungi and yeasts used in the manufacture of cheeses may also produce allergy in sensitized individuals. Baking powder may be used where yeast allergy is present, though it must be remembered that certain powders contain small amounts of egg and that some patients are sensitive to the bromates in such powders. In fact, when definite iodide or bromide sensitization exists, producing cutaneous lesions especially, it may be necessary to exclude all sources of them, such as baking powders and iodized salt from the diet. An unusual source of allergy is from dyes used in foods. When phenophthalein sensitization exists, productive as it is of many types of skin and mucous membrane lesions, all pink-colored foods and drinks should be excluded. Symptoms arising from other dyes in foods have been reported in the literature.

The reactions which arise in the same patient from biologically related foods were first reported by Vaughan. This is especially true of fruits, vegetables, fish and other sea food. Patients may be allergic to all pit fruits (Drupaceae), to all citrus fruits (Rutaceae), to apples and pears (Pomaceae), to potato and tomato (Solanaceae), or to carrots, parsnips, parsley, and celery (Umbelliferae). Such group sensitizations do not always exist. For instance, many patients sensitive to apples or oranges can take pears and grapefruit with no trouble at all. However, this tendency to group allergies must be remembered. The problem of patients sensitive to practically all fruits, or less frequently to all vegetables, offers a serious challenge. At times such foods are sufficiently denaturized by heat so that moderate amounts of enough of them, especially in the canned state, can be taken, and an adequate vitamin intake can be assured. At other times allergy does not exist to all biologically related foods, and a few can be taken to assure proper vitamins and minerals. In such patients, the challenge also arises to find some unusual vegetables or fruits as used by other nationalities to which our patients have not become allergic. Hawaiian taro, guava jelly, and arrowroot starch are examples. Increasingly, new foods of such types should be brought from Asia, Central and South America, and other lands, and made available for our people in America. The easy cultivation of avocados and dates here in America shows that

the growing of many other new foods will be possible. Reference to a compendium of edible plants, as published by Sturtevant, indicates the possibilities along this line, and has been discussed in my previous publications. Again considering the patient sensitive to most fruits and vegetables, the use of Vitamins A, B, C, D and G in pill or capsule form is distinctly indicated. It is usually imperative to insist on the taking of definite amounts of some of those foods to which the least apparent allergy is present. At the same time, an attempt to raise tolerance to the most important vegetables and fruits by the hypodermic administration of antigens containing the active allergens preferably from the fresh products themselves, prepared according to Coca's technique, is justifiable. The degree of success from such therapy is still uncertain in all cases.

A discussion of patients sensitive to many foods must also include the fact that *too frequently neurotic individuals acquire distastes and aversions and apparent idiosyncrasies to foods to such an extent that gradually such restricted diets are taken that severe nutritional damage develops.* The study of possible food sensitizations in patients must ever be made with this fact in mind. Moreover, certain patients who have several definite food allergies which have been uncontrolled for years, but which have directed their attention to the likelihood that diet in some way is responsible for their invalidism, develop odd habits of eating, or follow the suggestions of friends, quacks, or food faddists, with the final result that detrimental habits of eating are acquired which at times are hard to counteract. In such patients, it may be necessary to ignore the possible challenge of food sensitization until nutritional balance and an increase in weight are established. Later a study of the patient with trial diets or with the leukopenic index may be advisable.

At all times, undesirable weight loss and deficiencies in protein, mineral, and vitamin balance must absolutely be prevented. In the case of certain patients it may be better to suffer from the effects of actual or possible allergenic foods than to develop increasing invalidism through nutritional deficiencies. Not infrequently, moreover, patients must accept certain mild evidences arising from slight allergies to a few or many foods, particularly if the foods productive of major severe symptoms have been discovered. However, with a persistent endeavor to evolve a diet devoid of foods to which detrimental allergies exist, success is usually possible, and many severe or vague though invaliding manifestations and symptoms can fortunately be controlled.

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A Rare Case of Primary Liver Carcinoma in Liver Fluke Disease (Clonorchis Sinensis)

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THIS case reported is presented (a) because of the rarity of clonorchiasis in the United States, particularly in the East; (b) non-surgical biliary drainage was the diagnostic means of discovering the liver fluke when the stools were negative on examination for parasites; (c) to reaffirm the observation that non-surgical drainage is at present the most valuable palliative measure in the treatment of the disease, as well as a promising means of introducing directly a chemotherapeutic agent to be yet discovered in combating clonorchiasis.

The liver fluke, clonorchis sinensis, is found in many Asiatic countries, mainly China, Japan, India and Korea. In Central Japan certain areas are estimated to have an infestation incidence of as high as 67% of the population, according to Katsurada (1). On the East coast of India, the eggs have been found in as high as 50% of the natives by Leger (2). However, in a statistical study, Uttley (3) reported the incidence of clonorchiasis to be 13.9% in 367 consecutive post-mortems in Hong-Kong and Faust (4) in a careful study in Southern Korea found the infestation in 20% of the population.

The fluke inhabits the human biliary tree, (as well as that of the dog, cat, rat, pig, mouse, camel and badger). It is from 10-20 mms. long and 2-5 mms. broad, has an oral and ventral sucker, is characterized by a spineless cuticle, a short oesophagus, simple intestinal ceca, branched testes situated posteriorly, a trilobate ovary and moderately developed vitelline glands. The eggs are from 28-30 mu long and 15-17 mu broad, operculated, very dark, and have a ciliated miracidium within. Development outside the body takes place in two different intermediary hosts—the primary, a mollusc, and the secondary, several species of the carp fish (fresh water variety). Human infestation then occurs on eating this latter fish raw—as is a custom in certain sectors of the already mentioned countries.

In lighter infestations the symptoms vary and in-

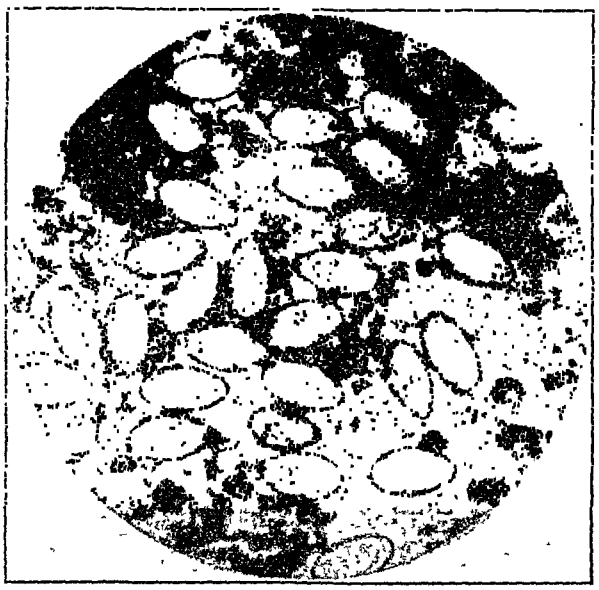


Fig. 1. Photomicrograph (approx. 400x) showing the eggs of the clonorchis sinensis as seen in the fluid obtained from biliary drainage. Note the operculum which is easily seen in several of the ova near the center; also the tiny spine at the opposite end. Within many of the ova the ciliated miracidium is plainly visible.

clude dyspepsia, epigastric and upper abdominal distress, unrelated to meals, and night blindness. When the disease becomes more advanced the liver descends below the right costal margin to varying size, recurring attacks of jaundice take place, and chronic diarrhea and vomiting are present. Late anasarca makes its appearance and a severe cachexia sets in which gradually terminates the disease fatally. Associated with this terminal picture, there is frequently a leukocytosis of over 30,000 and an eosinophilia of over 40%.

The underlying pathology of this infestation results from changes within the liver, brought about by the irritation of the adult fluke within the ducts. There results proliferation of the duct epithelium, with degeneration and necrosis of the periductile parenchyma.

If the infestation is heavy, small areas of necrosis of the liver 2 or 3 cm. in diameter may be seen which communicate with the ducts and contain many parasites. Later, marked periductile and interlobular cirrhosis occurs usually bringing about obstruction to the portal circulation. There follows enlargement of the spleen, chronic congestion of the gastro-intestinal tract with subsequent chronic gastro-enteritis. In some instances ascites may be present. Occasionally, biliary stasis results from obstruction of the ducts with transient jaundice. In a few cases, primary liver cell carcinoma (cholangioma) has been seen in association with the infestation. In rare instances, the pancreas may also be the site of the infestation with similar changes leading to fibrosis.

CASE HISTORY

A Chinese male adult, H. L., aged 47, was first admitted on 8/16/ 36 to the private service of Dr. John A. Kolmer at Temple University Hospital. The patient was formerly a resident of South China and had lived in this country for 21 years. His chief complaints were vomiting, pain in the upper right quadrant, loss of weight and general exhaustion, all of 6 weeks duration.

He was in good health prior to six weeks ago when he first experienced epigastric and upper right quadrant pain of variable duration after each meal. At this time, vomiting occasionally occurred on the ingestion of starchy foods, sour regurgitations and continuous belching were now present. Two weeks prior to admission vomiting occurred following each meal, associated with almost constant dull aching in the upper right quadrant. Scleral jaundice was simultaneously noted but was of transient nature. He had had mild diabetes 5 years previously which responded well to simple dietary management.

The only important physical feature during routine examination was the presence of an enlarged liver, extending approximately 5 cms. below the right costal margin; the abdomen was slightly distended. The patient appeared to be well nourished.

On admission his blood count revealed 6,750 leukocytes with 73% poly. neutrophils, 16% lymphocytes, 8% monocytes, 3% eosinophiles, 0% basophiles. The hemoglobin was 15 gms. or 89.55%; erythrocytes were 5,250,000 and of normal character, color index being 0.86. The urine was negative for sugar, but showed a very slight trace of albumin, and microscopically 2-5 hyaline casts per lower power field, occasional red blood cells and 0-7 leukocytes per high power field. The Icterus Index was 6 units, the van den Bergh gave a delayed—very weak direct reaction and the indirect van den Bergh estimation gave a reading of 0.25 mgms. The blood sugar value was 96 mgms. A stool study including culture made by an experienced bacteriologist showed no ova or cysts, no vegetative amoeba. A cholecystogram revealed insufficient gall bladder function but no evidence of gall stones. His T.P.R., except for the first day when a slight rise in temperature and pulse rate occurred, were essentially normal.

A non-surgical biliary drainage revealed a marked duodenitis and catarrhal cholecystodochitis. The eggs of the clonorchis sinensis (Fig. 1) were observed in the "B" and "C" fractions of the bile. Subsequently other biliary drainages were accomplished with essentially the same findings.

The clinical course continued with increasing enlargement of the liver, and persistent upper abdominal distress and weakness. The patient then left the hospital, sought treatment by Chinese herbalists, grew considerably worse and was readmitted two months later, with great exhaustion, persistent cough, great thirst and extreme dyspnea. At this time patchy rales throughout the lungs and marked

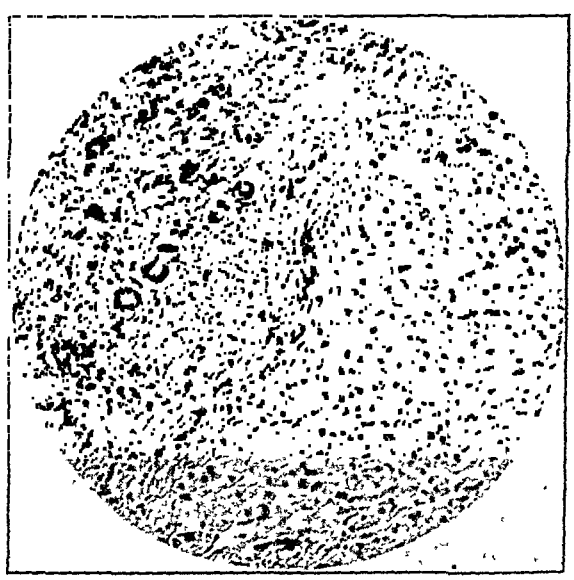


Fig. 2. Photomicrograph (approx. 100x) of a portion of the liver, showing marked interlobular and periductile fibrosis.

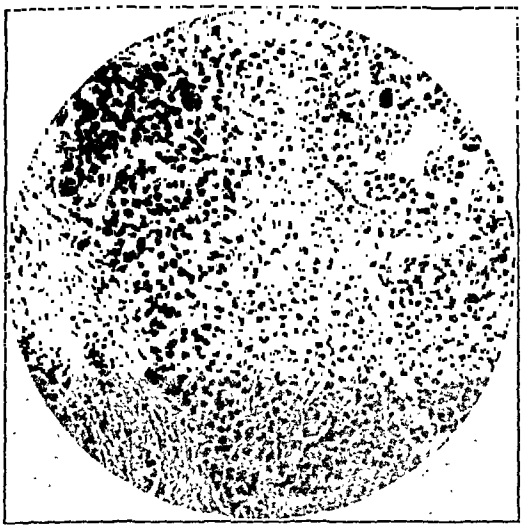


Fig. 3. Photomicrograph (approx. 100x) of an area in the liver showing the primary liver-cell carcinoma (cholangioma). No normal liver parenchyma is included in this photograph. Note the marked similarity of the arrangement of the tumor cells to the normal parenchyma. Observe the wide variation in size of the cells. The central portion shows degeneration and necrosis.

ankle and pre-tibial edema were present; the liver extended to the umbilicus, was tender to palpation and dehydration was considerable.

The blood sugar was 107 mgm., Plasma CO_2 26 volumes per cent; temperature was normal, pulse rate 108, respirations 30. The stools were now positive for the parasitic eggs, sputum examination was negative for the parasitic ova. His blood count revealed a leukocyte count of 9,300, of which 80% were poly. neutrophils, 10% lymphocytes, 7% monocytes, 2% eosinophiles and 1% basophiles. The hemoglobin was 12.5 gms. or 73.7%, erythrocytes 5,000,000, color index .73, the character of the erythrocytes were normal. The urine showed a slight trace of albumin, occasional red blood cells, but no casts. During the 6 days following admission, the temperature and pulse rate continued to rise, the sputum became bloody and coughing pronounced; marked weakness ensued, and the patient expired in the acute phase of the associated bronchopneumonia.

Complete necropsy was refused, but a stab biopsy of the liver was obtained. Histologically, this tissue showed (1) marked interlobular cirrhosis (Fig. 2); (2) areas of liver necrosis; (3) primary liver-cell carcinoma (cholangioma). (Fig. 3).

COMMENT

The importance and frequency of clonorchis infestation in certain sections of the Orient has been borne out. Following extensive histological studies in sixty-six livers infested with clonorchis sinensis, Hoeppli (5) corroborated the original work of the Dutch investigator Mebius (6) and showed that in many cases in which symptoms were light or non-existant, considerable histological changes were already present in the liver. He describes the increase in periportal tissue, fatty changes in the liver cells, extensive fibrosis, dilatation of bile ducts, with thickening of the walls and glandular proliferation. Typical Laennec's cirrhosis and parasitical portal cirrhosis is also reported.

In view of the two previous reports including a series of primary liver carcinomas in clonorchic livers (7, 8), it is possible that primary hepatic malignancy may be a sequel to the parasitic infestation, in addition to the parasitic cirrhosis and the hyperplastic cholangitis with chronic fibrous hepatitis which has already been described. The prolonged local physical irritation in addition to the toxic exudates may well be contributory factors in the production of the cancer.

It has been unfortunate that the work of various observers has tended to minimize the potential seriousness of clonorchiasis. This may be accounted for by (a) the long and drawn out course of the disease, and (b) the comparatively rare and scattered liver studies in clonorchiasis hepatis have been insufficient in impressing the significance of the terminal involvement of the clonorchic liver. It is because of these facts that the lack of therapeutic studies is to be greatly deplored in this not infrequent Oriental disease. To date there is not one drug which has shown any value in combating the parasite. The only therapeutic palliative measure has been the use of the non-surgical biliary drainage. To quote Bercovitz's (9) clinical studies in a large series of cases, "Biliary drainage yielded the most spectacular results in cases where the liver was enlarged and tense. Drainage continuously for a few days usually caused the liver to be reduced within the costal margin, and to all outward appearances the patient was "cured." However, in none of these cases did we ever finally rid the bile of ova." He then issues a warning against the use of the method of non-surgical biliary drainage by the untrained, because of the liability to shock and accidents. Filicene, benzol, emetine, oil of chenopodium, thymol, tetraiodophenolphthalein have been tried (10) but have proven failures. Calomel, urotropin and sodium salicylate have been attempted (11), as well as arsphenamine (12) and various other agents, unsuccessfully. Faust's use of gentian violet may prove of value but has not given definite results to date.

The importance of searching the bile in all cases of enlarged livers in patients coming from the Orient is emphasized by the fact that a careful stool examination by an experienced bacteriologist revealed no parasites or ova whereas on the following day, the ova were recovered from the biliary extractions. This is in agreement with Toullec and Riou (13) who were struck with the relatively infrequent finding of the eggs in the stools during life, as checked by post-mortem studies. They found that following duodenal intubation in all suspected cases of liver fluke infestation, the diagnostic incidence of clonorchis sinensis rose by leaps and bounds.

Since an attempt to halt the ingestion of improperly prepared fresh water fish or sea food by the natives of the Orient is obviously desirable but impractical, it would be a great service for Oriental research foundations and investigators to encourage therapeutic studies in this field.

Appreciation is herewith expressed to Dr. John A. Kolmer through whose courtesy this case is reported.

by the liver. From this, it seems that a reserve supply of concentrated bile, which may be discharged into the intestine in small amounts during the first 20 or 30 minutes after a meal, would have a favorable effect in initiating digestive processes in the intestine. In fact, the gall bladder bile is sometimes referred to by physiologists as "ignition bile."

If it can be established that the storage of bile for digestive purposes is a function of the gall bladder, it will be obvious that cholecystectomized patients, or patients with chronic disturbances of the biliary tract should be fed frequently with the idea of promoting the flow of bile by the liver, and thus keep it thin and moving as in animals where there is no gall bladder. That frequent feeding should be employed is an old clinical impression still held by some internists. But, such management will not generally be recognized as essential until its physiologic importance is proven. For example, formerly it was debated whether fats and acid fruits should be avoided by the patient with acute cholecystitis. Now, since it is known that fats and acids are potent excitants of gall bladder activity, doubt no longer exists.

In summary, the physiological evidence indicates that the chief function of the gall bladder is pressure regulation; but, the possibility that storage of bile for digestive purposes also occurs in those forms which concentrate bile, is one which cannot be easily dismissed. If the latter remains unproven, it may then be surmised that the gall bladder developed secondarily to the appearance of a sphincter at the junction of the common duct with the intestine to serve only the primary function of pressure regulation.

TABLE I

	Number of families recognized	Number of families investigated	Number of species investigated
AMPHIBIANS	19	11	16
REPTILES	55	12	70
BIRDS	161	84	171
MAMMALS			
Monotremata	2	2	2
Marsupialia	10	10	26
Insectivora	9	9	32
Dermoptera	1	1	2
Chiroptera	18*	13	59
Primates	9	9	66
Carnivora	10	10	65
Xenarthra	4	4	14
Pholidota	1	1	2
Tubulidentata	1	1	1
Artiodactyla	9	9	83
Sirenia	3	3	3
Hyracoidea	1	1	1
Proboscidea	1	1	2
Perissodactyla	3	3	9
Cetacea	9	7	19
Rodentia	25	24	89
Mammals, Total	116	108	495

*The families of bats missing are rare

ANATOMICAL EVIDENCE

Bearing the physiology of the gall bladder well in mind, it should be interesting to examine various vertebrate phyla for this organ, ascertain its presence or absence, and correlate with this evidence, other facts pertaining to the economy of the animal. Thus, diet, other modifications of the digestive tract, and even taxonomical relationships, may bear on the existence of the organ in an individual species.

Little effort has been made to describe variations in the form or anatomical relationships of the organ. Suffice it to say that this hardly seems necessary, insofar as the organ is either present or absent, and no series between these extremes can be easily demonstrated.

In the lower chordates, the liver, for the most part, is represented by groups of "hepatic caeca," which are intimately associated with the digestive tract. The liver is not consolidated into an organ, separate from the gut, and the gall bladder is not seen.

In vertebrates, the liver first becomes a distinct organ and with its development the gall bladder is first seen. In the Cyclostomata, primitive jawless vertebrates, the organ is present either in the larval or adult form, or both.

Most fish possess a gall bladder, but it may be occasionally absent. Those species lacking the organ are true bony fish (Teleostii). In the simpler forms (sharks, chimaeras), it is apparently constantly present, as it is in the lung-fishes (Dipnoi). This later group resembles in some respects, the ancestor of the amphibians, and it is significant that the organ is constantly present.

Amphibians apparently all possess the gall cyst. From Carboniferous amphibians, reptiles arose. The reptiles flourished abundantly throughout the Mesozoic, and gave rise to the predominant forms of our present fauna, i.e., birds and mammals. Like the amphibians from which they arose, all existing reptiles possess the gall bladder. It is highly probable that the organ was never lost here, even in herbivorous types, because of the intermittent feeding habits of this group, and because the organ is not known to be absent from any existing reptile.

Birds are closely associated with reptiles, and unmistakably derived from them. They arose at about the same time as mammals, but their adaptability has led to both a greater diversity of structure and a broader ecologic range. Although reptilian ancestory may be equally remote from both birds and mammals, the earlier success of birds has possibly allowed a more complete manifestation of those tendencies to vary, which are visible in mammalian evolution. The gall cyst is frequently absent in birds, and correlation of this fact with knowledge of diet and morphology offers no explanation. In no order of birds yet examined, is the organ constantly absent.

In this investigation, mammals are the main [illegible] of interest, because our end is to explain its [illegible] invariable presence in man.

Among the *primitive mammalian orders,* Monotremata and Marsupialia, the gall bladder is constant

kilo of body weight, per day. Man, however, only secretes 20 c.c. of bile per kilo per day.

The Physiologic Capacity of the Gall Bladder: Since the size of the gall bladder, the bile output, and the ability of the gall bladder to concentrate, varies in different animals, the *physiologic capacity* will vary. By this term is meant that fraction of the daily output of bile which the gall bladder is capable of storing; and, if it were known with certainty that this bile was stored for digestive purposes, this phrase would be appended to the definition. A contrast of physiologic capacity is demonstrated by man who can store the bile secreted during 12 hours, and a guinea pig which can store only the bile secreted for 12 minutes.

An Additional Function of the Sphincter: It should be considered that this structure probably prevents the regurgitation of duodenal contents into the common bile duct. This prevents ascending infection of the liver. It suggests that animals devoid of a competent sphincter should have some compensatory mechanism. Several such mechanisms do occur. There may be a one-way valve; large quantities of bile may keep the ducts flushed out; the extra-hepatic ducts may show peristaltic activity. Investigations show that the horse which lacks both a competent sphincter and a gall bladder has both a valve and a liver which forms large quantities of bile. On the other hand, the adult pigeon*, which also lacks a gall bladder has very motile ducts, and a liver forming relatively large quantities of bile.

The Practical Significance of the Problem: It is not generally agreed that the gall bladder serves the function of the storage of bile for digestive purposes. This is because physiological studies have not as yet demonstrated detectable disturbances of digestion or nutrition after cholecystectomy. However, when a gall bladder which concentrates efficiently is removed, certain changes are known to occur. These are: (a) incompetence of the Sphincter of Oddi with a variable return of competence; (b) dilation of the extra-hepatic ducts; (c) small areas of local necrosis in the liver. These changes certainly indicate that the gall bladder has a function, even if its general role is not to store bile for digestive purposes. Unfortunately, it is not known why all these changes occur, but dilation of the ducts is generally attributed to the return of competence of the sphincter. If this interpretation is correct, and if no direct digestive disturbances result from cholecystectomy, then the chief function of the organ in man, the dog, and the cat, for example, is to regulate the pressure in the extra-hepatic ducts, and this regulation is rendered necessary by the Sphincter of Oddi. Hence, from an evolutionary viewpoint, a gall bladder was developed secondarily to the sphincter, and the sphincter served primarily to prevent regurgitation from the intestine. However, given an animal whose liver produces relatively small quantities of bile, it is then reasonable to assume that such an animal might possess a better digestive apparatus if a gall bladder and a sphincter were present to render possible the storage of bile for digestive purposes. The following facts force the consideration of such an hypothesis: (a) bile plays an important role in the digestion and absorption of fats; (b) it is essential for the absorption of vitamin D and carotene, the precursor of vitamin A; (c) it plays a role in the absorption of iron and calcium; (d) all domestic animals that form a small quantity of bile have a gall bladder of large physiologic capacity; (e) the absorption of bile salts from the intestine augments the secretion of bile

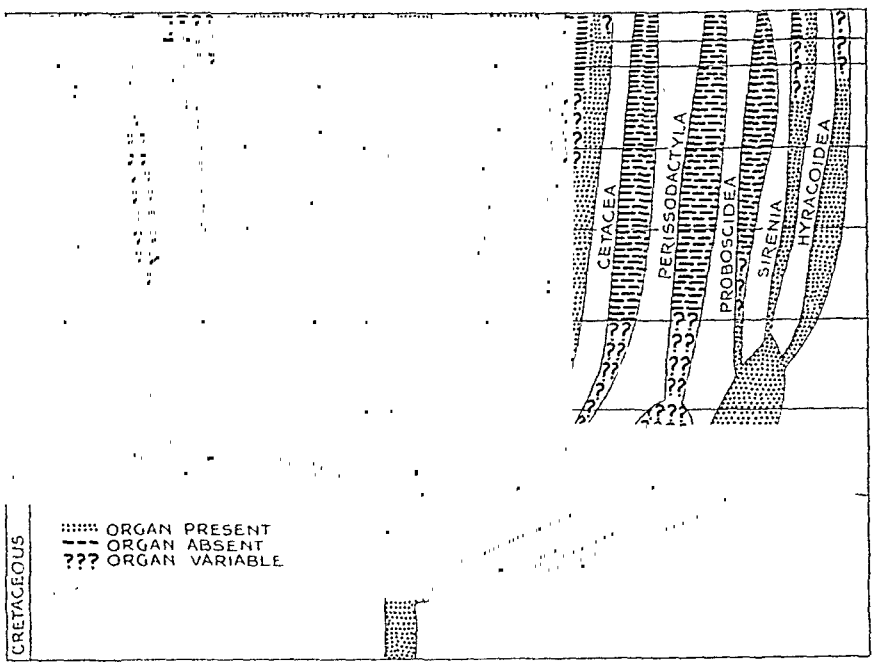


Fig. 1. Chronological distribution of existing placental mammals showing probable evolution of the gall bladder (after Romer).

*A gall bladder is seen in the embryo.

of a carnivorous animal of necessity offer only occasional meals, and these have generally a high fat content. From a physiological point of view, storage of concentrated bile should be of aid in the digestion of such meals, and it is significant that the organ is constantly present in these forms.

The absence or loss of the organ without harm or disturbance of survival value might be anticipated from the evidence of Schmidt and Ivy. They found species in which the organ had no apparent or demonstrable function. It may be said that the organ was "physiologically absent." Species possessing this type of a gall bladder are usually members of an order in which there are other species in which the organ is anatomically absent. *Further, the gall bladder is not absent from those species which have descended most directly, or with the least specialization in regard to body form, from the ancestor of mammals,* namely, insectivors.

Another factor which may influence the existence of the gall bladder in a given species is the proximity which this species has to the ancestral form. It will be noted* that those species, families, or orders which most closely resemble the ancestor of a given group tend constantly to retain the gall cyst, while those which vary most, tend to lose the organ. It is also very evident from our studies that the form and structure of the various portions of the gastro-intestinal tract are more readily changed in response to dietary habits than the gall bladder is lost.

The stable nature of the gall bladder suggests that it may be of value as a taxonomical characteristic. In only nine families was the organ found to be present in some members, and absent in others. In at least six of these the variation occurred between species or individuals. In the remaining three, it was possible to arrange sub-families, and here, for the most part, definite tendencies following the lines of arrangement were demonstrable. Individual variations in the organ are probably comparable to the anomalies occasionally seen in the human cadaver. The frequency with which these anomalies occur may be a measure of the declining "need" for the organ. Thus in the dissections of *Hyrax,* three observers found a gall bladder; five did not. With the giraffe on the other hand, the records show only two gall bladders out of about twenty dissections. From these records, it might be concluded that these animals will soon (in evolutionary time) lose the organ completely, and in all individuals.

It is interesting that closely related species particularly among the Muridae, may differ in the possession of the organ. *Besides this, the occurrence of anomalous absences in individuals of the same species suggest that it might be possible to study the mechanism of the inheritance of the organ and the physiological changes associated with its loss.*

CONCLUSIONS

1. The gall bladder is a typical vertebrate structure, found first in larval agnathostomes, and generally throughout the rest of the phyla.

2. All reptiles and amphibians have a gall bladder.

3. In birds the presence of the gall cyst is extremely variable, but carnivorous birds generally retain it.

4. The gall bladder is a primitive mammalian structure. It is not easily lost. It is not as readily lost as is the form and structure of the stomach, cecum and colon changed, i.e. a complex stomach may appear in a line of descent without the gall bladder being lost. It is usually retained in forms which most closely resemble the ancestral type; forms which vary most widely from the ancestral type may lose it.

5. Carnivorous mammals possess a gall bladder (except whales, *q.v.*), while mammals with other dietary habits may lose the organ. This apparently is related to the intermittent feeding habits of carnivorous types. Herbivorous forms with continuous feeding habits are most likely to lack the organ.

6. From the evidence of the dietary habits of cholecystous and acholecystous forms, one may conclude that if the gall bladder is removed from a given individual of any species, digestive efficiency will be diminished only if:

(a) the organ has a large physiologic capacity, and
(b) intermittent meals of a high fat content are given.

7. There is no anatomical evidence to indicate that the *Sphincter ductus choledochus* developed before a gall cyst. Yet the presence of such a sphincter renders a gall bladder essential as a pressure regulatory apparatus, unless the common bile duct manifests definite peristaltic activity as in the guinea pig, for example.

ADDENDUM

A point not referred to in our paper and which supports the concept that the gall bladder stores bile for digestive purposes should be mentioned.

If the sole function of the gall bladder is for the regulation of biliary tract pressure, why should the hormone, cholecystokinin, which is produced principally by the action of fats and acids, have been evolved. All hormones apparently manifest specific purposeful activities and the only purpose that cholecystokinin might serve is to evacuate the concentrated bile in the gall bladder when certain foods, particularly fats are eaten. The presence of the concentrated bile in the intestine would buffer acid, improve the digestion and absorption of fats and promote the formation of bile by the liver.

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A list of about 300 references will be found in the complete report of this study in the Field Museum Report

*Aplodontiidae, rodent ancestral family may be an exception.

present. These two orders, although in some respects highly specialized, have for the most part many affinities for their reptilian predecessors. It may be recalled that the monotreme is a duck-billed animal, oviparous, but nourishing their young on milk. The marsupials have a pouch which shelters their premature young. A true placenta is not found. The invariable presence of the gall bladder in these forms is interesting. Many of them are as highly specialized as the placentals, but among the placentals where the herbivorous type of diet has been assumed, the organ is absent in certain species. Remembering that monotremes and marsupials are rather low in the scale of mammalian evolution, it would seem that the gall bladder is a primitive structure not easily lost.

Most living mammals are placentals, and the development of the placenta along with other marked advances, accounts for the success of this group.

Primitive placentals are known to have lived at the end of the Age of Reptiles, and these forms were insectivorous. From them arose our existing placental fauna, and members referable to the same order (Insectivora) as those early forms still exist.

Closely related are four existing mammalian orders, the insectivors, the bats, the flying lemur, and the primates. They show definite relationships particularly in dental pattern, but specializations make them superficially unlike. The parent stem of these is the order *Insectivora*; moles and shrews are the best known of this group. Bats are closely related to the insectivors, and an intermediate type gives some hint as to how these may have been evolved. The flying lemur, *Galeopithecus*, is this transitional form. It is assigned to the order Dermoptera (Fig. 1).

Forms which were unseparable from insectivors by early workers, have now been assigned to the primates. They illustrate stages in the evolution of the primate type. The lemurs are excellent examples. From these simple forms have been derived the monkeys, apes, and finally man. Monkeys, however, diversified into two distinct lines. One, the New World Apes, is more primitive, while the Old World forms have diversified more widely. From the Old World family, man arose rather late in geologic history.

All these allied forms possess a common simplicity of structure, and are traceable to those insectivors which were the first placental mammals. They all possess a gall bladder.

Early in the Age of Mammals, other stem types were formed, some of these have perished and are known only as fossils; others gave rise to existing phyla. One of these stem types, known as the condylarth, was probably distinct before the end of the Age of Reptiles. From it came an order (Perissodactyla) which has a long paleontological history. The horse is the typical member. Neither it nor any of its close relatives, the rhinoceros and the tapir, possess a gall cyst (Fig. 1).

The amblypods, like the condylarths, were fairly distinct forms by the end of the Paleocene. From them, later in geologic history arose three orders which are represented by a rather diverse number of forms, the elephants, the sea-cows, and the hyraces. These species show a tendency to lose the gall cyst. It is constantly absent in the elephants, and is variably absent among the sea-cows and the hyraces (Fig. 1).

Carnivors, and through them the even-toed ungulates (Artiodactyla), arose later in paleontologic history from insectivorous forms. The carnivors constantly possess the gall bladder.

The artiodactyls at the present time are all herbivorous types, and some of them have lost the organ. All of them may eventually lose it, but its retention by some existing forms may be because of the proximity which these animals have to their carnivorous ancestors. Among the artiodactyls, the deer, peccaries, and duikers, have lost the organ; in the other forms it is usually present. In the giraffe, its presence is recorded in two out of twenty dissections; in the hippopotamus, its absence is recorded in one of four dissections.

The whales are said to have arisen from carnivorous forms early in the Eocene. They are highly specialized and morphological relationships are not clear. They all lack the gall bladder, but Weissberg (1932) has pointed out that a compensatory dilatation of the common duct with a valvular mechanism may exist. It is also possible that despite their intermittent feeding habits, the complex nature of the stomach may provide the duodenum with a continuous trickle of chyme, making concentrated bile less necessary for digestive purposes. Were the whales of proven herbivorous ancestry, one might point out that the sac-like reservoir in the common duct is a compensatory mechanism developed in an animal which had lost its gall bladder, and then changed its habits so that a compensatory structure was again necessary.

The Edentates are a heterogeneous group of mammals including three orders.

The order Xenarthra (armadillos, anteaters, sloths) is a New World group of unknown ancestry. The present fauna is meager, but at one time these forms predominated in South America. They all possess a gall bladder with the exception of the three-toed sloth, a vegetarian. Its absence in this individual is difficult to explain, but it seems significant that variation first occurs in this order in an herbivorous form.

The Aard-vark *(Orycteropus)*, and the Scaly Anteater *(Manis)* represent two orders (Tubulidentata; Pholidota), also of unknown ancestry. They are insectivors and both have gall bladders.

Rodents are the most successful of recent mammals. They were distinct during Eocene times. Most of them retain the gall cyst, but it is absent in some forms. Outstanding examples of species which lack the organ are gophers, kangaroo rats, common rats, and some porcupines. There may be variation among families or even genera, within this order. The Muridae is particularly chaotic in this respect. Rodents are, for the most part, herbivors.

The foregoing statements are based on a study on the number of the families and species shown in Table I.*

Where it was possible, an attempt was made to select the most representative species of each family.

DISCUSSION

From the above evidence, several facts are forthcoming. In the first place, it will be seen that the gall bladder is present in all insectivors and carnivores (except whales), and that it may be lacking among omnivorous or herbivorous forms. The dietary habits

*The complete data collected in the course of this investigation will be issued in a Publication of the Field Museum of Natural History, Chicago. Zoological Series.

incidence of 80%. The clinical gastro-intestinal symptoms were definitely more pronounced in the patients with obstructive lesions than in the group where infection alone was demonstrated. No cases of acute urethritis as a rule do not warrant critical attention but in the light of these findings, they must be given adequate consideration since great relief of digestive symptoms was afforded a number of patients by eradicating these seemingly trivial infections.

TABLE IV

Analysis of previous abdominal surgery performed on patients in this series affording no relief from symptoms

Case	Surgery	Subsequent Urologic Diagnosis
1	Gall Bladder, Appendix	Hydronephrosis; Ureteral Stricture
2	Appendix, Panhysterectomy, Postoperative Adhesions	Urethral Stricture, Atony of Bladder
3	Appendix	Stone in Rt. Ureter
4	Gall Bladder Appendix	Left Ureteral Stricture
5	Appendix	Prostatitis; Seminal Vesiculitis, Stricture Rt. Ureter
6	Appendix	Hydronephrosis from Aberrant Vessel at Ureteropelvic Junction
7	Appendix, Right Tube, Ovary	Ureteral Stricture, Megalo-ureter and Renal Pelvis
8	Gall Bladder, Appendix	Prostatic Hypertrophy, Renal Calculi
9	Appendix, Tubes; Postoperative Adhesions	Right Ureteral Stricture and Pyelitis
10	Uterine Suspension, Appendix	Nephroptosis
11	Appendix	Undescended Testicle
12	Appendix, Repair of Cervix	Right Pyelitis, Renal Ptosis

urinary tract infections were included in this study. A classification of the pathology found in the urinary tract is contained in Table V. Such conditions as trigonitis, seminal vesiculitis, prostatitis or posterior

TABLE V

Analysis of urologic pathology diagnosed in group of forty-eight cases

Stricture and Contracture of Urethra	15
Posterior Urethritis	3
Prostatitis	10
Seminal Vesiculitis	2
Prostatic Hypertrophy	2
Bladder Neck Contracture	2
Chronic Cystitis	1
Trigonitis	6
Undescended Testicle	1
Ureteral Stricture	11
Ureteral Kink	4
Ptosis Right Kidney (Marked)	6
Ureteral-lithiasis	1
Chronic Pyelitis	1
Congenital Stenosis of Ureteral Orifices or Ureteropelvic Junction	6

EXPERIMENTAL PRESENTATION

Other investigators have demonstrated both fluoroscopically and kymographically that changes in the muscular activity of the digestive tube are reflexly excited by disease of the urinary tracts. It has been assumed that these changes in muscular activity are probably responsible for the production of the associated digestive symptoms.

Tixier and Clavel (1) in a series of acute experiments upon dogs by means of kymographic tracings showed that exteriorization of the kidney, stimulation

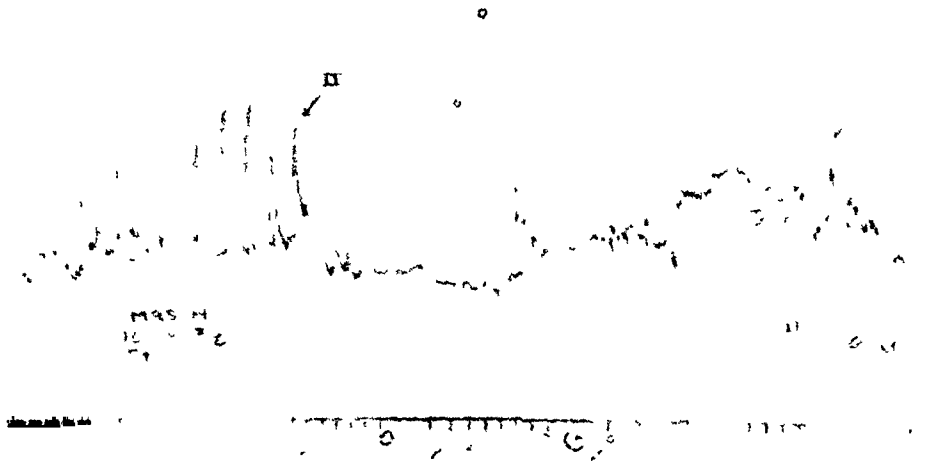


Fig. IA. Normal feeding reflex, human stomach. At point marked "2", patient was fed 4 oz. of milk and potato gruel. The tracing shows an immediate fall in tone and inhibition of peristalsis with a gradual restoration of tone occurring in about 25 minutes with a restoration of peristalsis. This constitutes the normal gastric appetite, or taste, reflex. It will be noted that the peristaltic rate is one complete contraction approximately every 2 minutes.

The Mechanism of Production of Digestive Symptoms Associated with Urologic Pathology

By

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DURING recent years, the authors, in common with many others, have observed the frequent occurrence of reflex digestive symptoms associated with and produced by urologic pathology.

While it has been generally assumed that these digestive symptoms were associated with disturbances of the muscular activity of the digestive tube, apparently the exact nature and location of some of these changes have not been reported. Accordingly, a clinical and experimental study was undertaken, (I) to show Clinically, that silent urologic pathology frequently is the exciting factor in the production of reflex digestive symptoms; (II) Experimentally, that these digestive symptoms are associated with and probably produced in part at least by certain changes in the muscular activity of the stomach, colon and probably duodenum and, (III) to postulate that the reflex changes observed in the muscular activity of the stomach and duodenum may be factors in the production of peptic ulcer.

CLINICAL PRESENTATION

The clinical aspects of the etiologic relationship of urologic pathology to reflex digestive disturbances have been exhaustively and competently presented by many observers. The probable nervous mechanism involved in the production of these viscero-visceral reflexes has been adequately recorded. This presentation is confined to an analysis of sixty cases consulting the gastro-enterologist because of digestive symptoms, subsequently referred to the urologists. Of this number, forty-eight patients were relieved by urologic diagnostic and treatment procedures.

The many and various symptoms presented by this group of patients have been abstracted and catalogued in Table I. Only ten of the forty-eight patients presented symptoms of urinary tract difficulties, unless pain in the flank might be considered as a specific urologic manifestation. There were four such cases.

In four cases no functional nor organic disease of the gastro-intestinal tract was demonstrated. Diagnoses of the gastro-enterologist are shown in Table II.

TABLE I

Tabulation of the symptoms of the forty-eight cases which responded to urologic treatment

Epigastric Distress	28	Eructation and Regurgitation	13
Precordial Pain	3	Nausea and Vomiting or Vomiting Alone	9
Diffuse Abdominal Pain	17	Heartburn	5
Pain Rt. Lower Quad	8	Diarrhea	3
Pain Lft. Lower Quad.	2	Anorexia	2
Pain Lft. Upper Quad.	1	Hunger Pains	2
Backache	6	Distention	1
Pain in Flank	4	Tachycardia	1
Pain in Thigh and Hip	1	Dysphagia	1
Pain Left Shoulder	1	Rectal Tenesmus	1
Urinary Symptoms	10		

TABLE II

Provisional gastro-enterologic diagnoses

Gastric Ulcer	2
Duodenal Ulcer	2
Gastric Hypermotility	7
Duodenal Spasm	2
Spasm at the Cardia	4
Pylorospasm	3
Ileal Regurgitation	7
Irritable Colon	8
Colon Stasis	11
Proctitis	3
Anal Sphincter Spasm	2
Diverticulosis	1
Abdominal Visceroptosis	5
Cholelithiasis	1

In this group of sixty patients, thirty-six, or 60%, showed changes in muscular activity of the digestive tract. It is interesting to note the types of motor disability of the digestive tube encountered. These varied from colon stasis to hypermotility of the stomach, spasm of the anal sphincter to spasm at the cardia.

TABLE III

Motor changes in the gastro-intestinal tube observed in forty-eight cases

Gastric Hypermotility	7
Duodenal Spasm	2
Spasm at the Cardia	4
Pylorospasm	3
Colon Stasis	11
Ileal Regurgitation	7
Anal Sphincter Spasm	2
Total	36

Of the forty-eight patients in whom definite urologic pathology was demonstrated, twelve patients had previously been subjected to abdominal surgery without relief of their symptoms.

Urologic investigation of these patients revealed that obstructive lesions along the urinary tracts predominated, being present in thirty-eight instances, an

*From Research Department of Jackson Memorial Hospital, Miami, Florida.

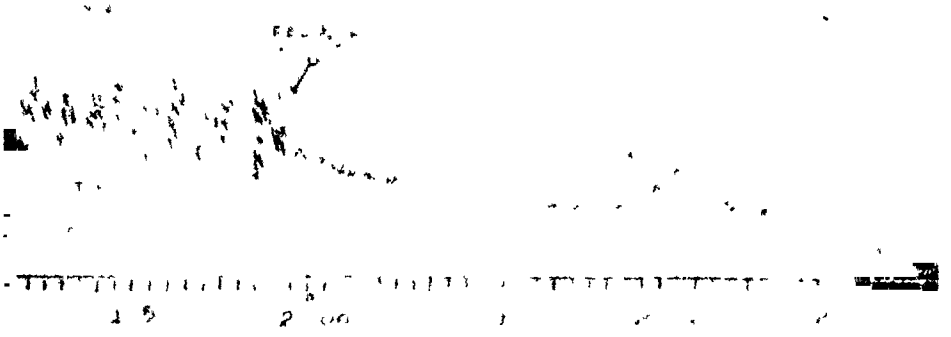


Fig. IIA. "Shows a normal gastric feeding reflex obtained by inserting a balloon through a permanent gastrostomy." At the point of feeding indicated by the arrow, there was an immediate inhibition of tone and peristalsis with reappearance of peristalsis in approximately 20 minutes. Note the close parallelism in the normal dog's stomach and the human stomach as shown in Fig. IA.

In another group of experiments, dogs were used. Gastrostomies were first performed. Later, we attempted to make a permanent ureteral fistula. In only one dog were we fortunate enough to have both a satisfactory gastrostomy and ureteral fistula.

In this dog, tracings were first made to show the normal gastric feeding reflex.

Later, a left-sided ureterostomy was made. This healed perfectly. There was no obstruction in the ureter and no apparent damage was done to the kidney.

Gastric tracings were made on a fasting stomach and the ureter was traumatized by twisting a catheter in the left ureter. The dog was then fed one ounce of ground cooked beef.

There was a momentary relaxation followed by an immediate and prolonged spasm of the gastric muscu-

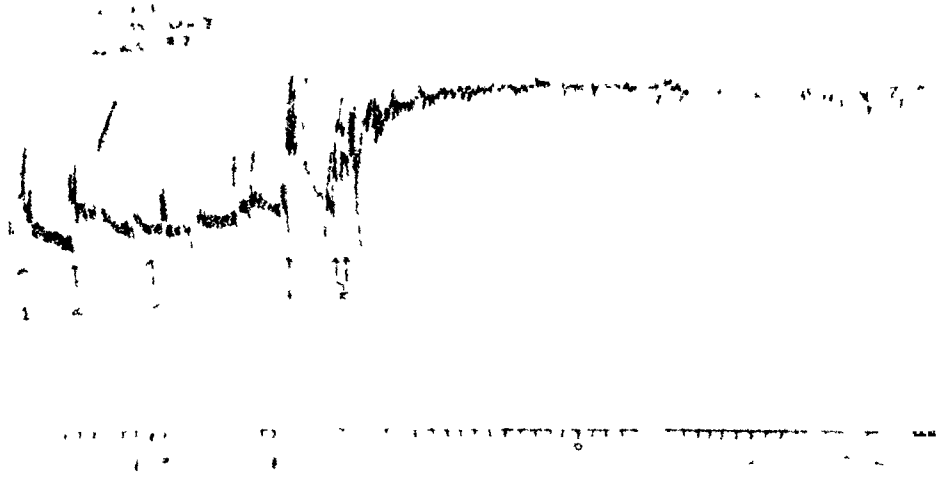


Fig. IIB. "Shows the inversion of the normal feeding reflex in the dog's stomach after ureteral trauma." At "1" catheter was inserted into the ureter. At "2", silver nitrate was injected and the catheter twisted. At "3", the catheter was withdrawn. At "4", the dog was permitted to smell food. The tracing shows an immediate increase in tonicity with superimposed peristalsis followed by relaxation. At "5", the dog was fed one-quarter pound of raw ground beef. Again, there was an immediate increase in tone with superimposed peristalsis. Thereafter, there was maintained a very high state of tonicity with small peristaltic waves. This tracing is almost exactly comparable to that of the human stomach, as shown in Fig. IB. The stomach was in complete spasm with almost complete obliteration of the lumen.

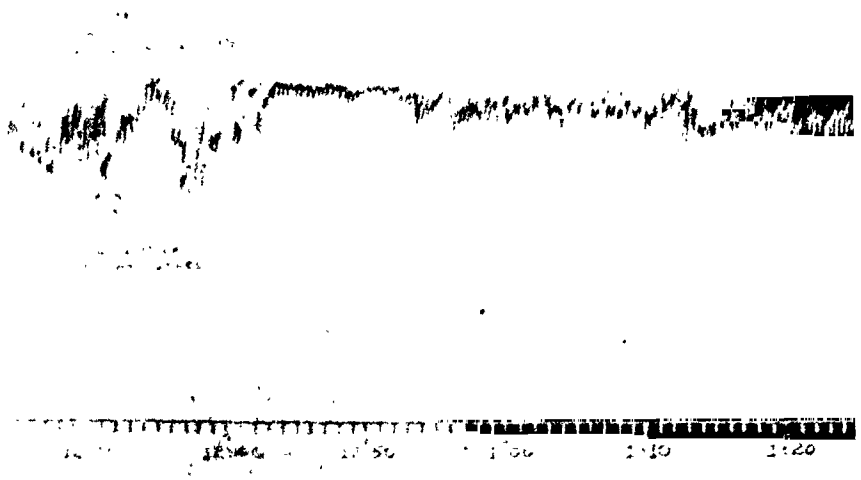


Fig. IB. "Showing inversion of the normal gastric feeding reflex in the human stomach associated with urethral and left ureteral stricture, symptomatically relieved by correction of the urologic pathology." It will be noted that before feeding and even after feeding the peristaltic beat is very rapid, as high as two peristaltic contractions occurring in one minute. At the point of feeding, an almost immediate increase in tone is noted followed by a temporary relaxation and again a continued very high tone. During the peaks of the contractions the lumen of the stomach was obliterated. It will be noted also in this tracing there was not an inhibition of peristalsis. This is the typical inversion of the normal gastric reflex.

of the kidney and stimulation of the kidney peritoneum caused an increase in frequency and amplitude of gastric peristalsis and produced tone changes in the colon. The latter consisted principally of immediate inhibition of tone and peristalsis. Unfortunately, these acute experiments did not simulate the conditions usually found clinically.

The conditions of the experimental work reported here were kept in as close an approximation as possible to the conditions usually encountered clinically. In this group of experiments, kymographic tracings were made upon the stomachs of dogs and humans and upon the colons of humans with preexisting or created urologic pathology.

CHANGES OBSERVED IN THE MUSCULAR ACTIVITY OF THE STOMACH REFLEXLY EXCITED BY UROLOGIC PATHOLOGY

It had previously been observed by one of us (2) that normally the gastric musculature relaxed immediately with the first taste of food—the normal feeding reflex (Fig. IA).

It was observed that in the presence of intra or extra gastric, abdominal pathology, this normal relaxation did not occur. Instead, with the first taste of food there occurred either a momentary relaxation followed by strong contraction, or an immediate increase in the tonicity of the gastric musculature with or without superimposed peristalsis. This contraction frequently amounted to violent and prolonged spasm which completely obliterated the lumen of the stomach. This constituted a complete reversal or inversion of the normal gastric feeding reflex. The degree of inversion or distortion was found to be approximately proportional to the severity of the symptoms encountered, and was not influenced by the character of the gastric secretions, establishing the changed muscular activity of the stomach as the probable source of symptoms.

This distortion of the gastric feeding reflex was usually associated with epigastric distress of varying degrees of intensity.

With this experience as a background, it was assumed that stimuli arising from lesions of the urologic tract probably produced similar changes in the muscular activity of the stomach. This was particularly indicated by the high incidence of the symptom of epigastris distress encountered with urologic disease as shown in Table I.

Kymographic tracings were made from the stomachs of two women with demonstrated urologic disease. A condom balloon was placed in the fasting stomach and connected by a duodenal tube to a recording device designed by one of us. This, in turn, recorded on a slow moving drum. The balloon was left in place long enough for the patient to become accommodated to its presence. The patient was then fed a cream of wheat and milk gruel and the changes in the feeding reflex were recorded. In both instances, there was found an increase in frequency and amplitude of gastric peristalsis and a marked inversion of the normal feeding reflex as shown in Fig. IB.

In this case, correction of urologic pathology resulted in complete subsidence of digestive symptoms. Unfortunately, with subsidence of symptoms, we were unable to obtain subsequent gastric tracings.

since three months after urologic treatment was instituted.

It is not assumed that disease of the urologic tract alone produces peptic ulcer but certainly the evidence indicates that it may in conjunction with other factors be an exciting cause in peptic ulcer production.

CHANGES OBSERVED IN THE MUSCULAR ACTIVITY OF THE COLON REFLEXLY EXCITED BY UROLOGIC PATHOLOGY

In this group, two women with permanent left-sided colostomies volunteered. Condom balloons were inserted into the proximal colostomy opening. The balloons were gently inflated with air and connected with the recording device in the usual way. The balloons were left in place for at least ninety minutes until the colon had accommodated itself to their presence. A cystoscope was then introduced without changing their supine position. A ureteral catheter was gently passed up the right ureter. The urethra, bladder and ureter were normal in each instance. ½ of 1% silver nitrate was injected into the ureter. The catheters were gently rotated and then withdrawn.

In both cases, introduction of the cystoscope and catheterization of the right ureter resulted in immediate inhibition of the muscular activity of the descending colon. Irregular tone changes followed until gentle trauma was supplied to the pelvis of the kidney and ureters. Trauma to the pelvis was accomplished by inserting the catheters up into the kidney pelvis. No reaction was noted in the colon. Introduction of ½% silver nitrate and/or twisting of the catheter in the ureter was immediately followed by a decrease in tone of the colon. Thereafter, for some time the tone changes were irregular until a late appearance (one-half hour) of increased muscular tone of the colon in both cases and increased tone and painful contractions at the site of the balloon in one case.

It is particularly interesting to note that in this one case, Fig. III, the patient had severe left-sided pain, occurring simultaneously with contractions in the colon, despite the fact that the right ureter was traumatized. It is probable that determination of the location of the painful contractions in the colon on the left side was due to the presence of the balloon, although the air pressure in the balloon did not equal one millimeter of mercury.

This experience suggests that the site of origin of symptoms arising in the colon are not associated with pathology in the ureter in the same side as suggested by Abeshouse (3) and Hartsock (4) and that possibly the local condition of the segment of the digestive tube is the determining factor in symptom production.

SUMMARY

A. An analysis is made of a series of forty-eight cases presenting digestive symptoms relieved by correction of preexisting urologic pathology.

B. Tabulations have been made of (1) The presenting digestive symptoms; (2) The gastro-enterologist's diagnoses; (3) Motor disturbances in various parts of the digestive tube which were found in 60% of the cases; (4) An analysis of twelve cases, or 27%, who had previous abdominal surgery without relief of digestive symptoms and who were subsequently relieved by correction of urologic pathology; (5) An analysis of forty-eight cases showing obstructive lesions of the urinary tracts in 80%; digestive symptoms were definitely more pronounced in this group.

C. Experimental studies of the muscular activity of the stomach and colon in humans and dogs showed that in the stomach, the rate of peristalsis was probably increased and that there was a marked inversion of the normal gastric feeding reflex associated with urologic pathology. In the colon, trauma of the urinary tracts produced a primary inhibition of tone and peristalsis followed by marked and irregular increases in tone and peristalsis. In one case, the colon contractions produced pain.

D. Evidence is produced which indicates that the side upon which the urologic pathology exists is not the sole determining factor as to the location of digestive dysfunction and pain, but that probably the local condition of the affected segment of the digestive tube is also a determining factor as to its location.

E. The marked changes in the muscular activity of the stomach and duodenum associated with urologic and other abdominal pathology may be factors in the production of peptic ulcer.

CONCLUSION

In view of the evidence presented in the voluminous literature and the clinical and experimental evidence presented here, it is obvious that it is incumbent upon the gastro-enterologist and internist to constantly keep in mind the high incidence of digestive symptoms excited by pathology outside the digestive tube, particularly in the urinary and genital tracts.

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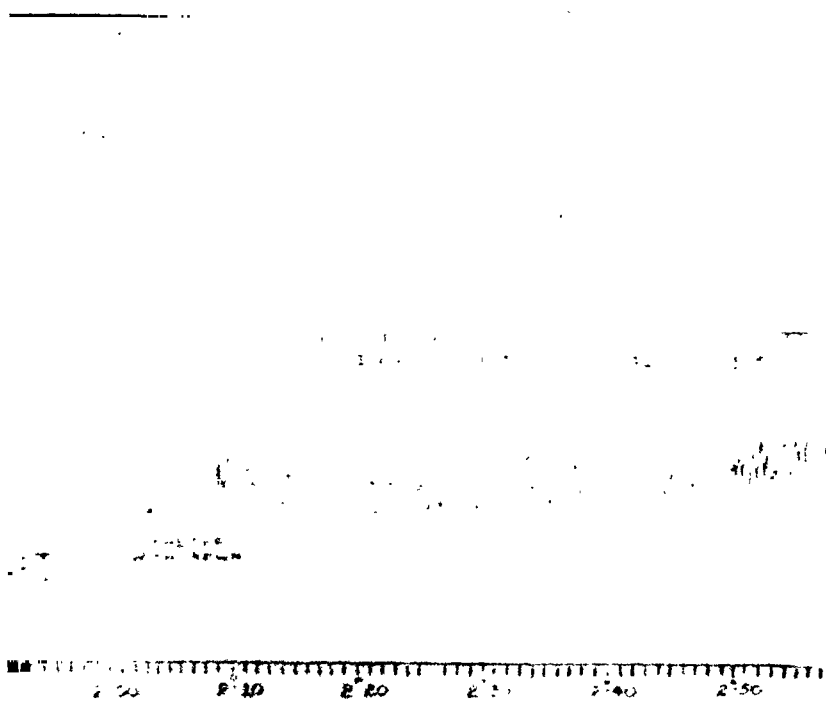


Fig. III. "Showing change in the muscular activity of the normal colon associated with trauma of the right ureter." The immediate effect of trauma to the right ureter was inhibition followed by a relatively late appearance of increased peristalsis and increased tone. The contractions in the colon shown from 2:20 on were accompanied by pain in the left side of the abdomen, with or without pain in the right flank.

lature. Apparently, the dog was distressed following the feeding as it became quite restless.

Comparisons of Figs. 1 and 2 show a striking similarity of reaction in the human and dog's stomachs.

Each tracing made of this dog's stomach after ureterostomy showed the same inversion of the gastric feeding reflex with a prolonged period of marked increase in tone following feedings. The balloon in the stomach was completely emptied upon removal during the period of high muscular tone, indicating a complete obliteration of the gastric lumen.

Fluoroscopic observations upon the duodenum and jejunum of many of the patients with urologic pathology has indicated that there is often a spasm of the duodenal cap and hyperperistalsis of the descending loop of duodenum, sometimes so marked as to cause regurgitation. No kymographic tracings have been made of the duodenum by the authors but clinical and X-ray observations have definitely demonstrated that there undoubtedly is an associated hypermotility and spasm of the upper small intestine reflexly associated with urologic pathology.

PROBABLE ETIOLOGIC RELATIONSHIP BETWEEN UROLOGIC PATHOLOGY AND PEPTIC ULCER

That urologic and other abdominal pathology excites intense and prolonged reflex spasm of the stomach certainly, and of the duodenum probably, cannot be doubted. That this spasm is complete enough to obliterate the lumen of the stomach has been demonstrated.

It is not unreasonable to assume that the severe squeezing of the mucosa of the stomach and probably that of the duodenum is sufficient to empty the blood vessels in the soft velvety mucous membranes and to produce a definite and prolonged local ischemia interfering with the nutrition and resistance of the affected mucosa and predisposing to ulcer formation, either secondary to infection or by direct digestion of the enfeebled, traumatized area.

It is difficult to understand why more ulcers do not occur when this type of trauma is present, as this distorted reflex is excited not once but at each regular meal, day after day, week after week and frequently month or even year after year.

Doubtless other conditions are necessary to be present for ulcer formation; remote infection, ulcer diathesis, allergy, faulty food habits, chemical or metabolic toxins, nerve lesions, absence of antipepsin, mental or emotional states, or other factors.

In this connection, it is not amiss to report one very theatrical case. Mr. A. B. had a duodenal ulcer more or less continuously for ten years. Finally, as a last resort, an investigation of his urologic tract was advised. Cystoscopy disclosed a congenital narrowing of both ureteral orifices. These were dilated and upon subsidence of his reaction to this measure, his digestive symptoms entirely disappeared. This particular individual was quite skeptical of his relief and endeavored by dietetic indiscretions and alcoholic excesses to reproduce his familiar digestive distress, without success. For three years, this man has been free from digestive disturbances. There is no X-ray evidence of duodenal ulcer now nor has there been

we have traced this mechanism through experimental hemorrhagic anemia in dogs. These animals were on a normal diet with no mineral restrictions or additions. Following hemorrhage, the dogs show a drop in blood iron and hemoglobin, the degree of which depends upon the amount of blood lost. In the course of a few hours after the blood loss, the copper content of whole blood is seen to rise rapidly to reach a peak two or three days later. Then as the iron and hemoglobin return to normal as a result of increased hematopoietic activity, the blood copper gradually is reduced again to its normal level. This inverse ratio between iron and copper is a very constant finding in induced hemorrhage in experimental animals.

TABLE I

Typical blood copper and iron curve for experimental hemorrhage in dogs

Sample No.	Date	Hemoglobin grams per 100 c.c.	Iron, mg. per 100 c.c.	Copper, mg. per 100 c.c.
1	11/6	14.11	46.28	0.115
	200 c.c. of blood removed from jugular vein			
2	11/7	12.27	41.13	0.158
3	11/9	12.02	39.31	0.170
4	11/12	13.25	44.40	0.162
5	11/13	13.42	44.99	0.155
6	11/18	13.56	47.46	0.150
7	11/24	13.28	46.52	0.125
8	11/25	14.15	47.48	0.122
9	12/5	14.81	49.64	0.122

In human subjects, hemorrhagic anemia as a result of massive bleeding from peptic ulcer affords an opportunity to compare the experimentally controlled mechanism in dogs with a similar clinical condition. It must be remembered, however, in interpreting the results that we are dealing with anemia superimposed on a pathological process and as a result the bodily intake of antianemic principles, iron, copper and other blood-building components may be delayed or altered through faulty assimilation and absorption. It must also be remembered that we are speaking here of acute, massive hemorrhage and not the chronic type which is often associated with peptic ulcers. The chronic bleeding type with loss of small amounts of blood over a long period shows a hypercupremia but it is not characterized by the sharp rise to a peak followed by the consistent descent which is seen in acute hemorrhage under adequate treatment.

In one human case of anemia following massive hemorrhage from an ulcer we were able to make analyses of blood samples at intervals from the time when the hemoglobin and iron were at their lowest until the normal values were again reached. This case with the exception of a few fluctuations compares very favorably with the response seen in the experimental anemias. The return to the normal iron and hemoglobin values was comparatively rapid under treatment. The behavior of the blood copper was the same as in the dogs, rising to a peak and gradually declining again to normal.

In three other cases it has not been possible to trace curves through to complete return to normal but in all cases the trend has been a reciprocal relationship between blood copper and iron, the copper dropping from a hypercupremia toward the normal at about the same rate that the iron content rose toward its normal.

The most likely conclusion to be drawn from the finding of a high blood copper content in almost all cases of anemia, is that the copper is brought into use from the body reservoirs to stimulate hematopoiesis.

CHART I

Blood copper and iron values after massive hemorrhage from ulcer in man

Sample No.	Date	Hemoglobin grams per 100 c.c.	Iron, mg. per 100 c.c.	Copper, mg. per 100 c.c.
1	12/10	10.74	34.12	0.164
2	1/3	12.57	42.14	0.156
3	1/5	12.46	41.77	0.145
4	1/15	12.66	42.43	0.156
5	2/6	13.20	46.23	0.143
6	2/20	15.12	50.69	0.140
7	4/16	16.32	54.75	0.145

Hemoglobin calculated from blood iron by the formula: Mg. of Fe divided by 3.35 equals grams of hemoglobin per 100 c.c. of blood (9).

The possibility of a copper anemia with an insufficient intake of copper and a depletion of the body stores has been suggested following some experimental work on rats and other animals (10). By maintaining these animals solely on a diet of milk collected in glass or earthenware containers and restricting the copper intake entirely over a considerable period of time, an anemia has been produced in which low blood iron and hemoglobin were accompanied by hypocupremia. This is theoretically and experimentally possible but our results with large numbers of anemias, as well as the work of others, indicate that the body storehouse supply of copper is exhausted only in very rare instances in human subjects.

Attempts to apply the results of experimentation on animals to man often lead to erroneous conclusions. The artificial conditions employed in making the diet copper-free for experimental animals cannot be practically applied to studies on human beings. Copper is present in ordinary drinking water. Any diet which approaches normal, including in it vegetables, fruits, meats, liver, pasteurized milk, and sea foods is comparatively rich in copper. The elevated blood copper in cases of massive bleeding from ulcers indicates that even with the restricted diet of the patient with gastric or duodenal ulcer, the body stores are not usually exhausted.

It seems, therefore, that hypercupremia represents a response to an emergency and that the mobilization of copper is effected to stimulate hematopoiesis and combat the anemia present.

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The Effect of Bleeding Ulcers and Hemorrhagic Anemia Upon Whole Blood Copper and Iron

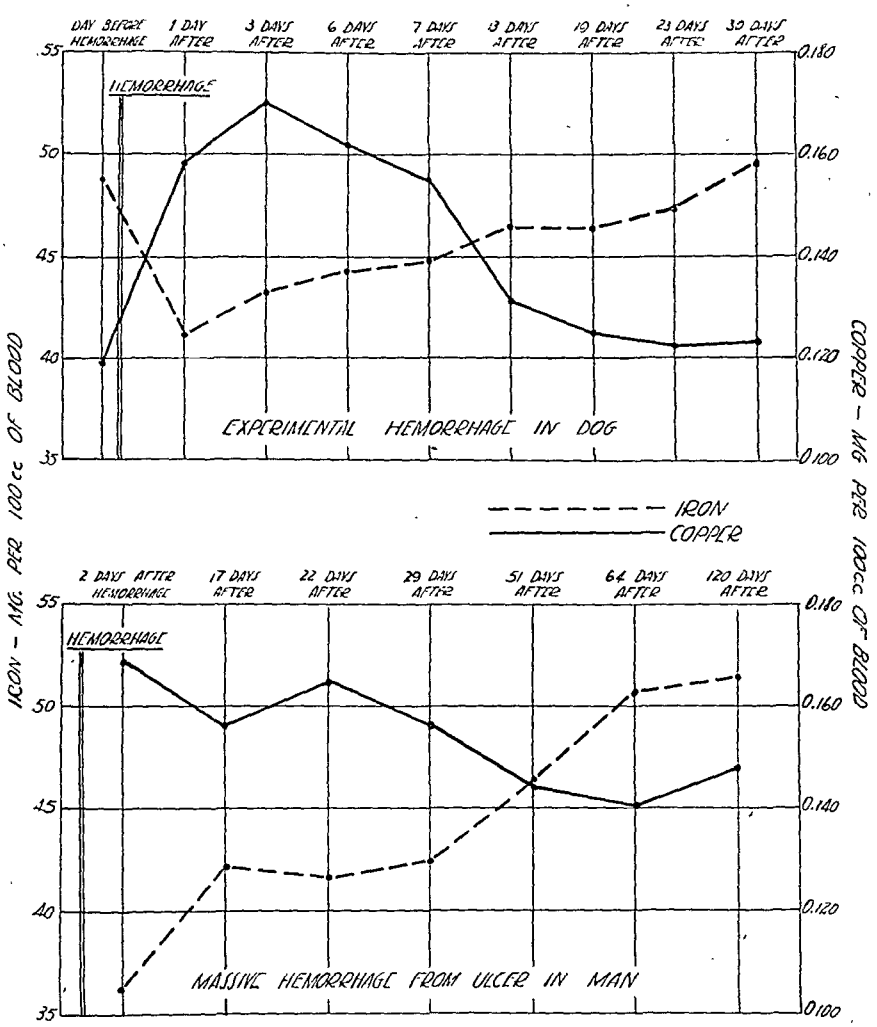
By

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COPPER is now definitely known to play a part in the mechanism of hematopoiesis although its exact role is not clearly understood. Experimental work and observation, however, indicate that it acts as a catalyst. Its presence makes possible the utilization of the building materials, iron and protein, necessary for the manufacture of hemoglobin and erythrocytes. Copper plays a direct part in red cell production (1) and catalyzes the conversion of stored iron into the hemoglobinous form (2, 3, 4, 5, 6).

Under normal conditions the amount of copper in whole blood shows remarkably little fluctuation. The average amount in the blood of adults is 0.132 mg. of copper per 100 c.c. (7), which appears to be the optimum for its catalytic role in normal hematopoiesis. However, in the event that the iron or hemoglobin content of the blood is reduced, the copper usually rises quickly. Hypercupremia is the usual response to hypoferronemia.



We have had occasion to see such response many times in analyses of blood taken from patients suffering from various types of anemia (7, 8). More recently

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chloride and ending at 0.38 per cent. (Normal is 0.44 per cent to 0.34 per cent). Other laboratory and X-ray work was negative.

Liver and iron were administered in large doses and eight blood transfusions were given, but the red count continued to drop. A month after admission the spleen became palpable and olive-green stools developed. The reticulocyte count at this time was 74 per cent.

In August, 1936, the blood examination showed the following: Red blood cells 580,000, reticulocytes 39 per cent, 15 normoblasts per 100 white cells, white blood cells 17,000 with 34 per cent stab forms, platelets 148,000. There were marked anisocytosis and hypochromia.

Following two blood transfusions a splenectomy was done under gas and ether anesthesia. Two more transfusions were given post-operatively. The jaundice began to disappear two days after the operation. and the red cell, hemoglobin, reticulocyte, and platelet counts began to rise. The patient felt much better and within a few weeks he was able to walk around the ward.

In October, 1936, the patient gradually became weaker, and the mild jaundice reappeared. The red cell count dropped to 1,200,000, the hemoglobin to 24 per cent, and the reticulocyte count to 28 per cent. Numerous transfusions were given, but he expired rather suddenly on October 18.

The spleen, removed at operation, weighed 560 grams. The capsule was thin and fairly smooth. The organ was doughy in consistency and on sectioning showed a dark red firm pulp, with fibrinous trabeculae and vessels which were retracted leaving a slightly puckered cut surface. The follicles were faintly visible and were grey in color. The microscopic section showed the malpighian bodies to be of normal size with well developed germinal centers. The arteries within the malpighian bodies were but slightly thickened and presented, occasionally, a slight hyalinization of the walls. The red pulp showed a marked congestion of the sinuses. The reticulum cells were scant. In many areas hemosiderin deposits were found. The trabeculae and splenic capsule were of normal appearance.

Post Mortem Examination: There was an enlargement of the liver due to infiltration by hematopoietic tissue. Smears of the bone marrow of the sternum, obtained by biopsy on August 14, 1936, and sections obtained from the bone marrow of the vertebrae, ribs, and sternum at autopsy on October 18, 1936, were examined by Dr. John Grill of the Department of Pathology. The morphological appearance of the bone marrow was very similar in all preparations. There were many closely packed, mature erythrocytes. Megakaryocytes were present, but not in an abundant amount. There were islands of closely packed normoblasts which contained dense, dark bluish stained, pyknotic appearing nuclei. Among the normoblasts there were megaloblasts with polychromatic cytoplasm, a reticular distinct chromatin network and in most instances without nucleoli. The cells of the leukopoietic series were found in normal proportions. Megaloblasts and myelocytes were scattered throughout sections and smears of the bone marrow. Eosinophilic myelocytes and metamyelocytes were quite outstanding in some places. There were also mature granulocytes.

The following tables show the important laboratory findings in these two cases:

DISCUSSION

The congenital form of hemolytic jaundice is usually much easier to recognize than the acquired type. The former pursues a long chronic course and usually no serious clinical manifestations arise. The acquired type may commence more abruptly and run a short stormy course leading to death within a period of a

CASE I

Date	R.B.C. c. mm.	W.B.C. c. mm.	Hb. %	Color Index	Lymphocytes %	Endothelial cells %	Reticulocytes %	Wass.	Icterus Index	Fragility of R.B.C. % of NaCl
9/10/30	1,670,000	4,000	35	1.0	34	3	19	Neg.	50	Began 0.46 Ended 0.32
9/27/30	1,550,000	7,800	27	0.97	17	4	16		38	
10/1/30	Splenectomy									
10/6/30	2,120,000	44,900	30	0.71	13	6	24		35	
10/22/30	2,370,000	13,550	33	0 75	33	9			15	
10/30/30	3,550,000	10,250	47	0.69	52	9	21		9	

CASE II

Date	R.B.C. c. mm.	W.B.C. c. mm.	Hb. %	Color Index	Lymphocytes %	Endothelial Cells %	Reticulocytes %	Wass.	Icterus Index	Fragility of R.B.C. % of NaCl
6/3/36	2,700,000	11,500	49	0.9	26	10	33	Neg	13	Began 0.50 Ended 0.38
6/27/36	1,660,000	20,900	45	1.2	26	7			21	
7/15/36	1,160,000	22,000	31	1.5	13	6	74		21	Began 0.50 Ended 0.44
8/3/36	920,000	10,800	27	1.5	35	4	10		20	
8/28/36	580,000	17,000	24	1.4	11	1	39		20	Began 0.50 Ended 0 30
9/3/36	Splenectomy									
9/17/36	1,530,000	12,800	39	1.3	31	5	3		13	
10/8/36	2,780,000	22,000	39	1 0	40	4	24		15	Began 0.50 Ended 0.32
10/17/36	1,200,000	38,000	24	1 0	2	14	28		16	

Acquired Hemolytic Jaundice*

By

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and

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HEMOLYTIC jaundice is a disease primarily due to increased fragility of the erythrocytes and characterized by anemia, increased destruction of red blood cells, acholuric icterus, splenomegaly, and a pronounced increase in the reticulocyte count. There are two forms of the disease, the congenital and the acquired, the first being the more common. The congenital type belongs to the inheritable diseases, occurring often in several successive generations, occasionally in several members of a family without cases among the ascendants, and also in a strictly congenital form, a single member of a family being affected from birth.

Imperfect accounts of the congenital form were given in 1885 by Murchison (1) and in 1890 by Wilson (2), but it was not until 1900 that the first accurate description was published by Minkowski (3). This was soon followed by articles in France by Gilbert, Castaigne and Lereboullet (4) and in England by Barlow and Shaw (5). Ten years later the condition was described in America by Tileston and Griffen (6) and shortly afterwards by Thayer and Morris (7). The true nature of the disease was little understood until 1907 when Chauffard (8) discovered the significant fact that the red cells showed a markedly diminished resistance to hypotonic salt solutions and reported (9) the presence of reticulated red cells in large numbers. Widal (10) was the first to describe the acquired type of the disease in detail and to recognize its hemolytic nature, although Hayem (11) had reported similar cases in 1898. The congenital form often is alluded to as the Minkowski-Chauffard type and the acquired form as the Hayem-Widal.

The following cases are presented because they demonstrate unusually severe grades of hemolytic jaundice and illustrate the pronounced contrast that may occur in response to splenectomy.

CASE REPORTS

Case 1. The patient was a white female, aged 41. She entered the hospital September 10, 1930, complaining of weakness, pain in the left upper quadrant and slight jaundice. The weakness started about six weeks before admission and became progressively worse. The week before admission she had three attacks of pain in the left upper quadrant which came on after eating and were relieved by vomiting. At this time she noticed that her skin and eyes were slightly yellow. There was no history of any food intolerance, hematemesis, or melena, but the stools were olive-green in color.

The family history was essentially negative.

The physical examination revealed a thin, white female, not acutely ill. She appeared anemic and was slightly jaundiced. The spleen was palpable and there was some tenderness in the left upper quadrant.

The blood examination on admission showed the red cell count to be 1,670,000, hemoglobin 35 per cent, color index 1.0, reticulocytes 19 per cent, white blood cells 4,000, polymorphonuclear cells 66 per cent, lymphocytes 34 per cent, platelets 130,000.

The icterus index was 50. The fragility of the red cells was increased, initial hemolysis beginning at 0.46 per cent of sodium chloride and ending at 0.32 per cent. (Normal is 0.44 per cent to 0.34 per cent). The urine was positive for urobilinogen. X-ray examination of the gastro-intestinal tract was negative. The van den Bergh reaction was indirect.

The patient was given liver and blood transfusions, but the red cell count rose only to 2,280,000 and the hemoglobin to 40 per cent.

A splenectomy was done. The spleen was found to be non-adherent and weighed 700 grams. It shrank to about one-half when removed. On pathological examination the malpighian bodies were distinctly visible. Microscopic examination showed that the follicles were not decreased. There was no fibrosis. There were relatively few lymphocytes, but an intense proliferation of endothelial leukocytes, many of them irregular in size and shape and some showing mitosis, were seen. The splenic pulp also showed a predominance of endothelial leukocytes. The liver was enlarged but smooth. The gall bladder was distended but no stones were felt.

A few days after operation a blood count showed the following: Red blood cells 2,120,000, hemoglobin 30 per cent, color index .71, reticulocytes 24 per cent, 7 normoblasts per 200 white blood cells, white blood cells 44,900, polymorphonuclear cells 83 per cent, lymphocytes 13 per cent, platelets 689,000. The jaundice began to decrease and finally disappeared. The patient felt much better and was discharged from the hospital October 30, 1930. The red cell count on discharge was 3,550,000, hemoglobin 47 per cent, white cell count 10,250, and reticulocyte count 21 per cent. This patient made an uneventful recovery and has remained well.

Case 2. The patient was a white male, aged 53, who entered the hospital June 3, 1936, complaining of progressively increasing dyspnea, mild jaundice, and generalized weakness. These symptoms began three months previously following a cold.

The family history was essentially negative.

Physical examination revealed nothing but a slight lemon-yellow tinge to the skin.

The examination of the blood on admission provided the following data: Red blood cells 2,700,000, hemoglobin 49 per cent, color index 0.9, marked anisocytyosis, reticulocytes 33 per cent, 4 normoblasts per 100 white cells, white blood cells 11,500, with 44 per cent stab forms, lymphocytes 26 per cent, monocytes 10 per cent.

The icterus index was 13 and the van den Bergh reaction was indirect. The urine showed urobilinogen but no bile. The fragility of the erythrocytes was increased, initial hemolysis beginning at 0.50 per cent of sodium

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few months. Failure to recognize and diagnose it is due in a large part to unfamiliarity of physicians with the disease. Although the clear cut text book type of case is distinctive, there are many cases presenting a clinical picture that may easily be confused with other types of blood dyscrasias and jaundice.

Acquired hemolytic jaundice may be secondary to some acute infection such as malaria, tuberculosis, or syphilis, but in most cases, as in those reported, the cause is not determined. The course of the disease may be acute, chronic, or chronic with periods of remission and relapse. Although the clinical picture of the acquired and congenital forms show striking similarity, there are some points of difference. Most outstanding are the episodes of pain and fever, the profound anemia, and the moderately intense jaundice which frequently accompany the acquired form, but are seldom noted when the disease is of the congenital type.

Acquired hemolytic jaundice is characterized by three major features, (1) splenomegaly, (2) anemia, (3) mild jaundice, and three minor features, (1) increased fragility of the red cells, (2) acholuria, (3) hyperreticulosis. The disease may begin with a sudden onset of violent pain, fever, and jaundice resembling that of a common bile duct obstruction, or it may begin insidiously with increasing weakness, anemia, mild icterus, and a sense of discomfort or pain in the left upper quadrant of the abdomen. Occasionally an enlarged spleen causing abdominal distress or a dragging sensation in the left side is the first symptom. During a crisis the spleen may enlarge considerably and then disappear under the costal margin when the exacerbation is over.

The jaundice of hemolytic icterus is usually mild. It deepens during a crisis, but never becomes dark brown as in a long standing obstructive jaundice. It is caused by an accumulation of the products of cell disintegration that the liver is unable to care for properly. A certain amount of altered pigment is absorbed into the blood stream.

The erythrocytes show increased fragility to hypotonic solutions of sodium chloride. Normal red cells show beginning hemolysis at about 0.44 per cent of sodium chloride and complete hemolysis at about 0.34 per cent. In hemolytic jaundice hemolysis may begin at 0.70 per cent of sodium chloride and be complete at 0.46 per cent or 0.50 per cent. Certain authors have looked upon the increased fragility of the red cells as being pathognomonic of the disease. In some cases, however, the fragility is normal especially where an extreme hyperreticulosis exists. Decreased resistance of erythrocytes is not confined necessarily to hemolytic jaundice.

The anemia varies greatly in different cases and at different times in the same case. Anisocytosis is usually quite marked, and there is a predominance of microcytes.

Reticulated red cells are greatly increased. Reynolds (12) reports a case in which the reticulocyte count reached 95 per cent. In his case the fragility of the erythrocytes was about normal, but he states that the large number of reticulocytes may have obscured the fact that the mature red cells were abnormally fragile. Some investigators believe that immature red blood cells, at least in certain disorders of the blood, are more resistant to hemolysis by hypotonic sodium chloride solution than the adult cells; others do not agree that this is true. Dreiling, Brody and Randall (13) reported a case in which the fragility test showed a beginning hemolysis at 0.5 per cent of sodium chloride and complete at 0.3 per cent on three occasions. At one time the reticulocyte count rose to 63 per cent.

Normoblasts are found occasionally, and polychromatophilia is often marked, but there is usually no granular degeneration. There are no characteristic changes in the leukocyte picture.

The stools are usually normal in color and consistency, but it is interesting to note that in the cases reported the patients developed olive-green stools at the same time that the spleen became palpable.

The absence of bile pigment from the urine (acholuria) in the presence of jaundice is usually found, but urobilin is often present. Giffen (14) reports a case of spontaneous hemoglobinuria in hemolytic jaundice. He found three other cases of this type in which the diagnosis of hemolytic jaundice was well established and an occasional case of questionable diagnosis that had been reported in German and French. He further states that from a study of both the clinical and the immunologic data, it seems justifiable to conclude that the hemoglobinuria of hemolytic jaundice is not due to syphilis, that it is not brought on by exposure to cold, and that the mechanism of hemolysis is not analogous to that in paroxysmal hemoglobinuria due to chilling.

Snelling and Brown (15) reported a case of a six year old child with hemolytic jaundice in which bone changes were found. The outer table of the skull was apparently gone and the diploe was in lines radiating out from the inner table with a very hazy appearance. The long bones were less dense than usual, and the growing ends, except the lower ends of the humerus, showed large spaces almost cystic in type between the trabeculae. The small bones of the hand showed this cyst-like arrangement to the fullest extent.

Bell (16) observed a case of a 15 year old male with acquired hemolytic icterus in which marked thickening of the skull occurred before splenectomy and the increase was about twice to three times normal thickness after splenectomy. This illustrates the marked activity and involvement of the bone marrow. No bones except the skull were involved in this process. Splenectomy brought about a permanent cure of the disease.

All of the symptoms of acquired hemolytic jaundice are subject to exacerbations sometimes accompanied by fever and always resulting in increased blood destruction. These exacerbations often follow dietary indiscretions, fatigue, or excitement. Occasionally one of the main symptoms of the disease, the increased fragility of the red cells, the splenomegaly, or even the jaundice may be absent.

DIFFERENTIAL DIAGNOSIS

In general these cases must be differentiated from other diseases accompanied by jaundice, splenomegaly, and anemia.

(1) *Diseases with jaundice:*

(a) Obstructive jaundice is excluded by the increased urobilin content, the absence of clay colored stools, and acholuria. Cholelithiasis is probably the most frequent source of error in the diagnosis of hemolytic jaundice because about 60 to 70 per cent of

other hemolytic agents, (4) a lessened tendency toward hemoglobinuria and jaundice after the administration of hemolytic agents, (5) a decrease in the volume of the portal blood, (6) the conversion of the bone marrow into red marrow and an actual increase in the volume of the marrow which can hardly be explained as merely compensatory to the anemia following splenectomy, and (7) the hypertrophy of the lymphatic tissues which seems to be due principally to hyperplasia of the endothelial cells.

The pathogenesis of the disease has been explained in two ways (25). One group of investigators (Widal, Vaquez and others) believe that it is essentially an increased fragility of the red cells, or, in other words, that the cause of the disease is to be found in a perversion of the function of the bone marrow so that it produces cells that are more easily fragmented than is normal. According to this theory, the splenomegaly is merely the reaction of the spleen to the presence in the blood of an increased number of cells that are ready for destruction. The other school (Minkowski, Chauffard and Banti) believe that the cause of the disease lies in the spleen. This organ for some reason becomes over-active and destroys more cells than it does under normal conditions. The latter view is strongly supported by the great improvement that follows splenectomy. The occurrence of occasional cases, typical in every respect except that the resistance of the red cells is normal, also points toward the splenic origin of the disease. However, neither of these theories is adequate to explain all of the findings.

Haden (26) gives a good explanation for the increased fragility of the red cells in congenital hemolytic jaundice, and since the process is somewhat similar in the acquired type it is worth while to give his conclusions. He finds that the diameter of the red cell in congenital hemolytic jaundice is decreased out of proportion to the change in volume, so it is apparent that the thickness of the cell must be increased and that the cell must tend to a spherical instead of biconcave shape. He made some experiments which indicate that the increased fragility is dependent on the spherocytosis or altered shape of the cells which affords a possible explanation for the increased hemolysis characteristic of the disease. He concludes that the red cells in congenital hemolytic jaundice constantly exhibit spherocytosis, best shown by the increased volume-thickness index. The diameter of the red cell in this condition is always less than normal, and the volume is variable. There is a direct relation between the volume-thickness index and the fragility. In congenital hemolytic jaundice the erythrocytes have at the beginning one of the shapes, through which a normal cell must pass when placed in successive dilutions of hypotonic salt solution, and so may be regarded as nearer the hemolysis point.

The pathogenesis of the jaundice seen in hemolytic icterus is best described by Rich (27). He classifies it as "retention jaundice" and states that it is recognized clinically by the following characteristics: (1) the bilirubin of the plasma which has never passed through the liver cells and is, therefore, unmixed with the constituents of the bile, gives the indirect van den Bergh reaction, (2) the stools contain an increased amount of urobilin because, in the face of the increased production of bilirubin, the liver is excreting more of the pigment than normally even though it cannot excrete enough of the excess to prevent jaundice, and (3) the urine contains an increased amount of urobilin but no bilirubin. It is free from bile salts which are formed in the liver and are absent from the urine unless they have been poured into the blood by the escape of whole bile from the canaliculi. Rich also states that jaundice resulting from over-production of bilirubin, in the absence of depressed liver function, rarely if ever occurs, because of the great reserve excretory power of the liver and because bilirubin is, as far as we know, formed only from the hemoglobin of destroyed red cells. Therefore an excessive formation of bilirubin is associated with an excessive destruction of red cells and an attendant depressing effect of anemia upon the liver. In hemolytic jaundice, in which there is an over-production of bilirubin, there is an anemia which depresses the excretory power of the liver. He also suggests that reticulocytes, which are present in high percentage, require more oxygen for their own metabolism than mature red cells, and may not be able to supply the tissues with oxygen as readily. This may be another factor in a depressed excretory function of the liver.

PATHOLOGY

Thompson (28) studied the spleens of thirty cases of typical hemolytic icterus and states that they all presented the same definite and characteristic changes. He describes the spleen of the typical hemolytic jaundice case as weighing 1000 to 1500 grams. It is usually easily removable at operation, being relatively free from adhesions. On section the fresh spleen presents a uniform and fairly characteristic appearance. The cut surface is relatively dry, dark purplish-red in color, and homogeneous in texture, bulging slightly above the capsule. The malpighian bodies are seen.

Thompson states that the microscopic appearance is uniform in all instances. The malpighian bodies are small and far apart. The venous sinuses are enlarged, widely separated, and frequently empty. The sinus endothelium is prominent, and the outline of these cells often bulges into the lumina of the sinuses. The pulp is a mass of closely packed red cells and this diffuse infiltration is the most striking feature of the microscopic appearance. There is no increase of connective tissue and no visible increase of iron pigment. The so-called iron incrustations are frequently encountered, usually within the trabeculae. There is no visible evidence of phagocytosis of the red cells, and, except for an occasional lymphocyte, one finds nothing but red cells distending, distorting, and dilating the pulp. He concludes that hemolytic jaundice is a definite clinical and pathological entity and that no difference exists between the congenital and acquired types.

PROGNOSIS

Since hemolytic jaundice is a disease of the reticuloendothelial system (25) it would be unreasonable to suppose that there would be no recurrences following splenectomy. A number of authors have called attention to this possibility and have seen cases where recurrence developed. Usually, however, the characteristic exacerbations do not return after splenectomy. The jaundice promptly disappears. In the absence of the spleen, red cell disintegration takes place in various remote areas of the body, probably in the bone marrow and possibly in the hemolymph nodes. Under

the cases are complicated by gall stones. Pemberton (17) reported on 118 cases of hemolytic jaundice, in which splenectomy was done, between 1908 and 1931, at the Mayo Clinic, and found conclusive evidence of disease of the gall bladder, with or without stones, occurring as a secondary complication in 68 per cent of the cases. Many patients have been operated upon for cholelithiasis, under the mistaken belief that the jaundice was of the obstructive type. The van den Bergh test is an aid in differentiating between hemolytic and obstructive jaundice.

(b) Acute infectious diseases with jaundice. In yellow fever and spirochetal jaundice, icterus is the outstanding feature. Jaundice is not uncommon in pneumonia and streptococcal septicemia. In these diseases it is probably hemolytic in origin.

(c) Familial icterus of the new-born is a very rare disease in which several children of a family are afflicted with deep jaundice shortly after birth. They usually die within a few days.

(2) *Diseases with splenomegaly:*

(a) Banti's disease or splenic anemia. Cirrhosis of the liver is usually present in the later stages of this disease and reticulated red cells are not abundant. Jaundice is not often present.

(b) In Gaucher's disease or large-celled splenomegaly there is a yellowish discoloration of the skin, but true jaundice is lacking. The spleen is enormously enlarged and the liver less so. A moderate anemia may be present.

(c) Syphilis of the liver may be accompanied by great enlargement of the spleen, but usually jaundice is absent. Syphilis may lead to true acquired hemolytic jaundice. The results of the fragility test and of anti-syphilitic treatment will lead to a correct diagnosis.

(d) Cirrhosis of the liver in the early stage does not show much enlargement of the spleen or jaundice except in the Hanot's type. Here the liver is much enlarged and jaundice is present. Portal cirrhosis is characterized in the late stages by ascites, hemorrhages and signs of collateral circulation.

(e) In chronic malaria the spleen may be considerably enlarged, but except in acute attacks, there is usually no jaundice.

(f) Tropical diseases with splenomegaly. Kala-azar is diagnosed correctly by finding the organism, Leishmania Donovani, in the material obtained by puncture of the liver or spleen.

(g) In leukemia the examination of the blood usually makes the diagnosis, but the occurrence of aleukemic leukemia must be remembered.

(h) In Hodgkin's disease the lymph nodes are enlarged and jaundice is absent.

(i) Polycythemia rarely is accompanied by jaundice, and the red cells are increased in number in contrast to the anemia that accompanies hemolytic jaundice.

(j) Diseases of infancy with splenomegaly. One must remember von Jaksch's anemia, rickets, tuberculosis, and hereditary syphilis. In congenital obliteration of the bile ducts the jaundice is of the obstructive type.

(3) *Diseases with anemia:*

(a) Pernicious anemia is characterized by macrocytosis, and there is no increased fragility of the erythrocytes.

(b) Acute hemolytic anemia, described by Lederer (18), is characterized by sudden onset, fever, leukocytosis and severe anemia.

(c) Idiopathic hypochromic anemia is characterized by microcytosis, low hemoglobin, and low color index. Usually there is no jaundice.

PATHOGENESIS

Despite the mystery that has surrounded the spleen in the past and the ignorance that still persists (19) regarding the exact nature of its physiologic functions, two important activities are now definitely established as centering in this organ. (1) the storage of red and white cells, (2) the phagocytic destructive activity of the reticulo-endothelial elements, the clasmatocytes of the splenic pulp, for the old or injured erythrocytes, granulocytes and blood platelets. Under physiologic conditions there is maintained a nice balance between bone marrow hematopoiesis and these splenic functions of cell storage and death. Krumbhaar (20), in 1923, proposed the term "hemolytopoietic equilibrium" for this balance. He states that bone marrow, spleen, liver, lymph nodes, and reticulo-endothelial apparatus combine to regulate the formation and destruction of blood cells in what may be termed the "hemolytopoietic system."

It has been the experience in medicine that, whenever any physiologic function is recognized for an organ, a disease entity due to a corresponding pathologic dysfunction, may be anticipated, and sooner or later will be encountered. Specific clinical entities involving disturbances in the functions of the spleen are known.

Another function attributed to the spleen (21) is the production of lymphocytes. It seems probable, that under some pathologic conditions, the endothelial cells and leukocytes may multiply and produce anti-toxins to counteract toxic substances brought to them. The most striking example of this is seen in typhoid fever.

During exercise (22), and in certain pathologic conditions, the spleen extrudes blood into the circulation to maintain circulatory balance. The ancients believed that the spleen had some relation to exercise and thought that the wind of runners was improved by splenectomy. The basis for this idea is not known. It may have been due to the prevalance of malarial splenomegaly, for this condition would obviously have an influence on exercise. The work of Barcroft (23) on the volume of the spleen indicated that the contents are expelled into the circulation during exercise.

The spleen seems to be the leading organ in the iron metabolism of the body (24); but just how this iron, derived from the breaking down of red cells, is carried from the spleen and formed into bile pigments has not been discovered since no free hemoglobin has been recognized in the splenic vein. It is probably tied in some way to the cells so that it is difficult to prove its presence. The spleen, like the rest of the reticulo-endothelial system, seems to be active in storing foreign coloring material as well as body-produced coloring matter. The endothelial cells of this system also have an intimate relationship to the metabolism of lipoids.

The important effects of experimental splenectomy (22) may be summarized as follows: (1) the occurrence of secondary anemia, (2) the production of leukocytosis, (3) the increased resistance of the erythrocytes to hypotonic sodium chloride solution and

Studies on the Control of Gastric Secretion*

I. Drugs Acting on the Autonomic-Sympathetic System. II. Drugs Acting as Central Emetics.

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and

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IF some relatively innocuous agent or procedure could be found that would abolish or greatly diminish the secretion of acid by the stomach, it should be of value in the treatment of peptic ulcer. In an attempt to understand more completely the control of the secretion of hydrochloric acid by the stomach, and with the idea in mind that some method might be obtained to produce temporary anacidity, the effect of a number of substances on gastric secretion in man and dog has been studied. These substances include:

I. Drugs acting on the autonomic-sympathetic system
   - A. Atropine
   - B. Bellafoline
   - C. Novatropin
   - D. Methatropin
   - E. Ergotamine

II. Emetics
   - A. Apomorphine
   - B. Apocodeine
   - C. Emetine
   - D. Quinine

METHOD OF EXPERIMENTATION

Experiments were performed on dogs with Pavlov pouches and on patients with chronic duodenal ulcer. Two types of gastric stimulants were used—food and histamine. Fractional test meals of crackers and water, and subcutaneous injections of 0.5 mgms. of histamine (ergamine acid phosphate, "Imido-Roche") were employed as the gastric secretory stimuli in fasting patients. The dogs were fed 200 grams of meat, 200 c.c. of milk, and 200 c.c. of water, or given 1 mgm. of histamine subcutaneously. Samples were withdrawn from the stomach of the patients every ten minutes for two hours before and after the test meal or histamine injection, and for seven hours from the pouches of the dogs after a meal, and for two hours before and after histamine. The acidity of the stomach contents was determined by titration with 0.1% Normal NaOH, Topfer's reagent and phenophthalein being used as indicators.

Drugs acting on autonomic-sympathetic system: Atropine, Bellafoline, Novatropin, Methatropin.

All who have observed the action of atropine (1) on gastric secretion in animals agree that the secretion is checked in all its normal phases. The literature has been reviewed recently by Gray (2) and an analysis of the mode of action of atropine on the parietal cell has been made. By using strictly controlled quantitative methods, it was shown that atropine decreases, but does not abolish, histamine stimulation of the parietal cell.

We find a difference of opinion as to the effect of atropine in man. Porter (3) found that the volume of gastric secretion was reduced after atropine, but that the free acidity was not changed. Others have found that the volume of secretion was reduced but that the free acid was higher (Klumpp and Bowie, Polland, Kalk and Siebert (4)). Keefer and Bloomfield (5) found that "not only was the total amount of secretion diminished, but the type of secretion curve was markedly altered." Rehfuss (6) found that the "psychic phase" was reduced, but that atropine did not abolish secretion. Winkelstein (7) found that atropine depressed the primary phase, and "also acts to suppress somewhat the chemical phase." Klein (8) says that in dogs all three phases of gastric secretion can be abolished by atropine, but in man the chemical phase cannot be suppressed. Roberts, Lockwood and Chamberlin (9) found that atropine reduced acidity and they thought that the regurgitation of bile caused by relaxation of the pyloric sphincter might neutralize the acid and cause the decrease. Others believing that atropine reduced gastric acidity clinically were Riegel, Bergmann, Mathieu, Schmidt, Chiari, Moore and Kilroe; Bennett, Loeper and Fau; Rall, Schiff and Kellerman; and Hernando (10). Bastedo (11) and Palmer (12) thought that it depressed gastric secretion only when untoward side actions were present, and Bastedo says that in the small doses which are used in man atropine is practically without effect on gastric secretion. Crohn (13) studied two patients with normal secretion periods. He found a slight rise of average total acidity when he gave one milligram atropine by hypodermic injection forty-five minutes after a meal. In two patients with continuous secretion he found that atropine stopped the secretion in an hour, and reduced the average total acidity. The same dose of atropine by mouth was ineffective. He also used belladonna until side actions were manifest. A test meal then showed an increase of average total acidity from 85.3% to 104.5%. The duration of secretion was decreased, however, to three hours. A careful study of the methods used in human subjects will reveal that most of the inconsistencies are due to differences in atropine dosage, differences in duration of the test period and the time of injection of the atropine, and differences in criteria used for determining inhibition of secretion. If doses adequate to dry the mouth are given, the total HCl output by the stomach is always decreased, the acidity may not change, or may increase or decrease.

Clinically both atropine and belladonna have been used extensively to reduce gastric secretion. In experimental work on gastric secretion in man and dogs, atropine has been generally used. We wondered if all of the belladonna principles supposedly present in proprietary products might prove more effective than the atropine derivative alone. We therefore attempted to compare the effects of atropine with one of the proprietary products of belladonna, namely *bellafoline*, in man and in the dog.

RESULTS

Table I shows the results of a comparison of the effect of subcutaneous injections of atropine or bellafoline on the gastric secretory response of the Pavlov pouch to histamine. Ten experiments were done with

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other hemolytic agents, (4) a lessened tendency toward hemoglobinuria and jaundice after the administration of hemolytic agents, (5) a decrease in the volume of the portal blood, (6) the conversion of the bone marrow into red marrow and an actual increase in the volume of the marrow which can hardly be explained as merely compensatory to the anemia following splenectomy, and (7) the hypertrophy of the lymphatic tissues which seems to be due principally to hyperplasia of the endothelial cells.

The pathogenesis of the disease has been explained in two ways (25). One group of investigators (Widal, Vaquez and others) believe that it is essentially an increased fragility of the red cells, or, in other words, that the cause of the disease is to be found in a perversion of the function of the bone marrow so that it produces cells that are more easily fragmented than is normal. According to this theory, the splenomegaly is merely the reaction of the spleen to the presence in the blood of an increased number of cells that are ready for destruction. The other school (Minkowski, Chauffard and Banti) believe that the cause of the disease lies in the spleen. This organ for some reason becomes over-active and destroys more cells than it does under normal conditions. The latter view is strongly supported by the great improvement that follows splenectomy. The occurrence of occasional cases, typical in every respect except that the resistance of the red cells is normal, also points toward the splenic origin of the disease. However, neither of these theories is adequate to explain all of the findings.

Haden (26) gives a good explanation for the increased fragility of the red cells in congenital hemolytic jaundice, and since the process is somewhat similar in the acquired type it is worth while to give his conclusion. He finds that the diameter of the red cell in congenital hemolytic jaundice is decreased out of proportion to the change in volume, so it is apparent that the thickness of the cell must be increased and that the cell must tend to a spherical instead of biconcave shape. He made some experiments which indicate that the increased fragility is dependent on the spherocytosis or altered shape of the cells which affords a possible explanation for the increased hemolysis characteristic of the disease. He concludes that the red cells in congenital hemolytic jaundice constantly exhibit spherocytosis, best shown by the increased volume-thickness index. The diameter of the red cell in this condition is always less than normal, and the volume is variable. There is a direct relation between the volume-thickness index and the fragility. In congenital hemolytic jaundice the erythrocytes have at the beginning one of the shapes, through which a normal cell must pass when placed in successive dilutions of hypotonic salt solution, and so may be regarded as nearer the hemolysis point.

The pathogenesis of the jaundice seen in hemolytic icterus is best described by Rich (27). He classifies it as "retention jaundice" and states that it is recognized clinically by the following characteristics: (1) the bilirubin of the plasma which has never passed through the liver cells and is, therefore, unmixed with the constituents of the bile, gives the indirect van den Bergh reaction, (2) the stools contain an increased amount of urobilin because, in the face of the increased production of bilirubin, the liver is excreting more of the pigment than normally even though it cannot excrete enough of the excess to prevent jaundice, and (3) the urine contains an increased amount of urobilin but no bilirubin. It is free from bile salts which are formed in the liver and are absent from the urine unless they have been poured into the blood by the escape of whole bile from the canaliculi. Rich also states that jaundice resulting from over-production of bilirubin, in the absence of depressed liver function, rarely if ever occurs, because of the great reserve excretory power of the liver and because bilirubin is, as far as we know, formed only from the hemoglobin of destroyed red cells. Therefore an excessive formation of bilirubin is associated with an excessive destruction of red cells and an attendant depressing effect of anemia upon the liver. In hemolytic jaundice, in which there is an over-production of bilirubin, there is an anemia which depresses the excretory power of the liver. He also suggests that reticulocytes, which are present in high percentage, require more oxygen for their own metabolism than mature red cells, and may not be able to supply the tissues with oxygen as readily. This may be another factor in a depressed excretory function of the liver.

PATHOLOGY

Thompson (28) studied the spleens of thirty cases of typical hemolytic icterus and states that they all presented the same definite and characteristic changes. He describes the spleen of the typical hemolytic jaundice case as weighing 1000 to 1500 grams. It is usually easily removable at operation, being relatively free from adhesions. On section the fresh spleen presents a uniform and fairly characteristic appearance. The cut surface is relatively dry, dark purplish-red in color, and homogeneous in texture, bulging slightly above the capsule. The malpighian bodies are seen.

Thompson states that the microscopic appearance is uniform in all instances. The malpighian bodies are small and far apart. The venous sinuses are enlarged, widely separated, and frequently empty. The sinus endothelium is prominent, and the outline of these cells often bulges into the lumina of the sinuses. The pulp is a mass of closely packed red cells and this diffuse infiltration is the most striking feature of the microscopic appearance. There is no increase of connective tissue and no visible increase of iron pigment. The so-called iron incrustations are frequently encountered, usually within the trabeculae. There is no visible evidence of phagocytosis of the red cells, and, except for an occasional lymphocyte, one finds nothing but red cells distending, distorting, and dilating the pulp. He concludes that hemolytic jaundice is a definite clinical and pathological entity and that no difference exists between the congenital and acquired types.

PROGNOSIS

Since hemolytic jaundice is a disease of the reticuloendothelial system (25) it would be unreasonable to suppose that there would be no recurrences following splenectomy. A number of authors have called attention to this possibility and have seen cases where recurrence developed. Usually, however, the characteristic exacerbations do not return after splenectomy. The jaundice promptly disappears. In the absence of the spleen, red cell disintegration takes place in various remote areas of the body, probably in the bone marrow and possibly in the hemolymph nodes. Under

these circumstances, the products of red cell destruction reach the liver by a longer route and in a less concentrated form. The liver is better able to take care of the material, and jaundice results only when red cell destruction has reached a higher degree than is necessary to cause it when the spleen is present. The resistance of the red cells returns to normal in a large number of cases. Frequently, even though the patient is clinically cured, this resistance of the red cells remains unchanged. Lord Dawson (32) of England, reported a case of hemolytic jaundice in which Spencer Wells did a splenectomy in 1887. The patient was twenty-seven years of age at that time. She recovered and the jaundice permanently disappeared. In 1931 the patient was still in good health for her age. A few years previous to this, her blood was examined and the fragility of the red cells was found to be still increased. The reticulated red cell count returns to normal. There seems to be no change in the patient's resistance to bacterial infection following removal of the spleen.

Giffen (22) reports a total of 81 cases of hemolytic jaundice in which splenectomy was done with a hospital mortality of only 4.39 per cent.

The prognosis in the acquired type is less favorable than in the congenital form because death in many instances results directly from the anemia or from intercurrent infections.

TREATMENT

In spite of the fact that X-ray has been beneficial in the treatment of hemolytic jaundice, splenectomy is the only therapeutic measure worthy of consideration. Some men have questioned the advisability of such a serious procedure in mild cases, but splenectomy is to date the only curvature method of dealing with the disease. As Krumbhaar (20) said, "It is in hemolytic jaundice par excellence that splenectomy has had the greatest success." The operation, according to Hurxthal (29), is effective because it removes the organ of red cell destruction, even though it does not remove the real cause of the disorder, the fragility of the red corpuscles. It should not be done during an acute exacerbation.

Reifenstein and Allen (30) reported three cases of chronic hemolytic jaundice that showed definite clinical improvement with liver extract, but they believe that further observations are necessary before definite conclusions can be drawn. Martin (31), on the other hand, states that hemolytic jaundice responds to but one form of therapy—surgery. He has found that liver extract is unavailing and that whole blood transfusions are superfluous in view of the rapidity with which the blood count increases to normal after operation. Our experience with liver extract in the two cases reported shows it to be of little value.

SUMMARY

(1) The chief clinical manifestations of acquired hemolytic jaundice are outlined and discussed.

(2) Two typical cases of the disease are presented. The ineffectiveness of medical measures in the treatment of these cases is pointed out. One patient was cured by splenectomy. In the other case, amelioration of the symptoms occurred immediately after operation but within several weeks there was a relapse which resulted in the patient's death.

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Studies on the Control of Gastric Secretion*

I. Drugs Acting on the Autonomic-Sympathetic System. II. Drugs Acting as Central Emetics.

By

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IF some relatively inconsequent or procedure could be found that would abolish or greatly diminish the secretion of acid by the stomach, it should be of value in the treatment of peptic ulcer. In an attempt to understand more completely the control of the *secretion of hydrochloric acid by the stomach*, and with the idea in mind that some method might be obtained to produce temporary anacidity, the effect of a number of substances on gastric secretion in man and dog has been studied. These substances include:

I. Drugs acting on the autonomic-sympathetic system
   - A. Atropine
   - B. *Belladonna*
   - C. Novatropin
   - D. Methatropin
   - E. Eupentamine

II. Emetics
   - A. Apomorphine
   - B. Apocodeine
   - C. Emetine
   - D. Quinine

METHOD OF EXPERIMENTATION

Experiments were performed on dogs with Pavlov pouches and patients with chronic duodenal ulcer. Two types of gastric stimulants were used—food and histamine. Fractional test meals of crackers and water, and subcutaneous injections of 0.1 mg. of histamine hydrochloride acid phosphate, "Merck Reagent," were employed in the gastric secretory studies on factory patients. The dogs were fed 200 grams of meat, 250 c.c. of milk, and 200 c.c. of water, or given 1 c.c. of histamine subcutaneously. Samples were withdrawn from the stomach of the patients every ten minutes for two hours before and after the test meal or histamine injection, and for seven hours from the pouches of dogs after a meal, and for two hours before and after histamine. The acidity of the stomach contents was determined by titration with 0.1 N. Normal NaOH, Topfer's reagent and phenolphthalein being used as indicators.

Drugs acting on autonomic-sympathetic system. Atropine, Belladonna, Novatropan, Methatropin.

All who have observed the action of atropine (1) on gastric secretion in animals agree that the secretion is checked in all its normal phases. The literature has been reviewed recently by Gray (2) and an analysis of the mode of action of atropine on the parietal cell has been made. By using strictly controlled quantitative methods, it was shown that atropine decreases, but does not *abolish*, histamine stimulation, of the parietal cell.

We find a difference of opinion as to the effect of atropine in man. Porter (3) found that the volume of gastric secretion was reduced after atropine, but that the free acidity was not changed. Others have found that the volume of secretion was reduced but that the free acid was higher (Klumpp and Bowie, Polland, Kalk and Siebert (4)). Keefer and Bloomfield (5) found that "not only was the total amount of secretion diminished, but the type of secretion curve was markedly altered." Rehfuss (6) found that the "psychic phase" was reduced, but that atropine did not abolish secretion. Winkelstein (7) found that atropine depressed the primary phase, and "also acts to suppress somewhat the chemical phase." Klein (8) says that in dogs all three phases of gastric secretion can be abolished by atropine, but in man the chemical phase cannot be suppressed. Roberts, Lockwood and Chamberlin (9) found that atropine reduced acidity and they thought that the regurgitation of bile caused by relaxation of the pyloric sphincter might neutralize the acid and cause the decrease. Others believing that atropine reduced gastric acidity clinically were Riegel, Bergmann, Mathieu, Schmidt, Chiari, Moore and Kilroe; Bennett, Loeper and Pau; Ball, Schiff and Kellerman; and Hernando (10). Bastedo (11) and Palmer (12) thought that it depressed gastric secretion only when untoward side actions were present, and Bastedo says that in the small doses which are used in man atropine is practically without effect on gastric secretion. Crohn (13) studied two patients with *normal secretion periods. He found* a slight rise of average total acidity when he gave one milligram atropine by hypodermic injection forty-five minutes after a meal. In two patients with continuous secretion he found that atropine stopped the secretion in an hour, and reduced the average *total acidity. The same dose of atropine* by mouth was ineffective. He also used belladonna until side actions were manifest. A test meal then showed an increase of average total acidity from 85.5° to 104.5°. The duration of secretion was decreased, however, to three hours. A *careful study of the methods used in human subjects will reveal that most of the inconsistencies are due to differences* in atropine dosage, differences in duration of the test period and the time of injection of the atropine, and differences in criteria used for determining inhibition of secretion. If doses adequate to dry the mouth are given, the total HCl output by the stomach is always decreased, the acidity may not change, or may increase or decrease.

Clinically both atropine and belladonna have been used extensively to reduce gastric secretion. *In experimental* work on gastric secretion in man and dogs, atropine has been generally used. We wondered if all of the belladonna principles supposedly present in proprietary products might prove more effective than the atropine derivative alone. We therefore attempted to compare the effects of atropine with one of the proprietary products of belladonna, namely *bellafoline*, in man and in the dog.

RESULTS

Table I shows the results of a comparison of the effect of subcutaneous injections of atropine or bellafoline on the gastric secretory response of the Pavlov pouch to histamine. Ten experiments were done with

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each dosage on two dogs. The pouch secretion over a two hour period was reduced by about 50% in each case. The height of titratable acidity was only slightly reduced and the total acid output in milligrams for

TABLE I

Showing effects of atropine and belladonna on the secretory response of the Pavlov Pouch to histamine (averages of 10 experiments with each dosage on 2 dogs)

	Total Vol. Output c.c.	Maximum Free Acid Clinical Units	Total Acid Output in mgms.
1 mgm. histamine (control)	21	119	97
2 c.c. bellafoline*	10.9	103	36
4 c.c. bellafoline	9.2	101	31
1 mgm. atropine	10	110	35
2 mgm. atropine	8	97	27

*2 c.c. of "bellafoline ampule solution" contains 1 mgm. of levorotatory belladonna alkaloids.

the two hour period was about thirty-three per cent of the usual histamine response. There was no essential difference in the effect of bellafoline or atropine. Because of the systemic effects of dryness of the mouth produced by atropine and the relatively large dosage necessary in the dog to reduce the gastric secretory response to histamine, we attempted a comparison of one of the more recent products, namely *novatropin*. Table II shows the effects of novatropin and of atropine on the gastric secretory response of a Pavlov pouch to histamine. There is a reduction in the volume secreted over a two hour period of about fifty per cent, but only a relatively slight decrease in the height of the titratable acidity. The decrease in volume, however, accounts for a considerable diminution in the total mgms. of acid secreted over a two hour period.

The effects of atropine and novatropin on the pouch secretion after a standard meal were also studied. Table III shows that the titratable free and total acidity were slightly diminished, but there was a considerable reduction in the volume over an eight hour period with consequent marked diminution of the total milligrams of hydrochloric acid secreted. Two milligrams of atropine were as effective as five milligrams of novatropin.

It should be pointed out that the drugs were injected just after the ingestion of the meal. The secretion during the first few hours is abolished or markedly depressed, the major portion of the secretion being collected in the later hours. In the dog atropine given at intervals markedly reduces the secretory response to a meal.

TABLE II

Showing effects of atropine and novatropin on the secretary response of the Pavlov Pouch to histamine

	Volume c.c.	Maximum Free Acid— Cl. Units	Maximum Total Acid— Cl. Units	Total mgm. HCl
1 mgm. histamine controls—Average of 20 experiments on 2 dogs	19	123	141	80
2.5 mgm. novatropin 1 mgm. histamine—Average of 14 experiments on 2 dogs	9	94	110	29
2 mgm. atropine 1 mgm histamine—Average of 10 experiments on 2 dogs	8	97	116	27

TABLE III

Showing effects of atropine and novatropin on the secretory response of the Pavlov Pouch to a meal (average of 10 experiments on 2 dogs)

	Volume c.c.	Maximum Free Acid— Cl. Units	Maximum Total Acid— Cl. Units	Total mgm. HCl
Controls with standard meals	127	142	165	685
2 mgm. atropine	57	134	146	271
5 mgm. novatropin	60	139	149	288

A comparison of the effect of atropine, bellafoline, novatropin and methatropin was made on eight patients with duodenal ulcer. The drugs were administered fifty minutes before giving 0.5 mgms. histamine as a gastric stimulus. The stomach contents were aspirated completely at ten minute intervals for two hours after the histamine injection. Table IV shows the average results. There was no effect on the height of titratable acidity reached, but the volume of secretion was diminished over the two hour period. Atropine reduced the volume and milligrams output of hydrochloric acid as effectively as any of the newer proprietary products in the dosages used. While it may be unfair to compare these drugs in the dosages used, systemic effects such as dryness of the mouth and skin, blurring of vision, or a sense of fullness in the head occurred with all drugs used in doses adequate to depress the HCl output.

We therefore do not believe that we can obtain satisfactory reduction of gastric acidity in man with any of the belladonna derivatives without producing untoward side reactions. In man the drugs of the bella-

TABLE IV

Showing the effects of atropine, novatropin, methathopin and bellafoline on the gastric secretory response of patients with duodenal ulcer to histamine

Composite averages of 8 patients	Volume c.c.	Maximum Free Acid Cl. Units	Maximum Total Acid Cl. Units	Total mgm. HCl
Histamine control	349	96	101	614
Atropine 1 mgm.	237	94	100	423
Novatropin 2.5 mgm.	263	98	104	534
Bellafoline 2 c.c. (1 mgm. levu-rotatory belladonna alkaloids)	300	96	102	585
Methatropin 10 mgm. (orally)	290	100	106	556

donna group used causes a diminution of the output of hydrochloric acid; but the concentration of the acid produced at the height of stimulation is not significantly diminished. In the dog the relatively larger doses, although producing dryness of the mouth, apparently do not produce toxic cerebral effects; the relatively larger dose of atropine given the dog depresses gastric secretion more.

It has been thought that histamine acted on the gastric cell, and atropine on the nerve ending. But since atropine does have some effect on the secretory response to histamine, it must act on the cell in addition to acting on the nerve ending. Brain and nervous tissue, however, are more susceptible to atropine poisoning than gastric tissue, and therefore we obtain toxic symptoms before we obtain achlorhydria in man.

CONCLUSION

Our findings with atropine are in accord with those of Keeton, Koch and Luckhardt (1) in the dog, and of Kiefer and Bloomfield (5) and Porter (3) in man. We noted a slight rise in the height of titratable acidity after atropine as did Polland (4), but the diminished volume of secretion always yielded a lower output of acid for the period of study. In order to obtain a depression of gastric secretion, the drug had to be given in amounts that caused dryness of the mouth. Atropine was as effective as any of the newer proprietary substitutes.

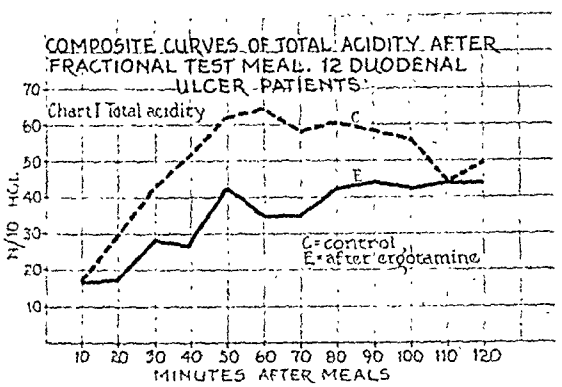
ERGOTAMINE

Volborth and Kudriawzeff (14) have claimed to have demonstrated the presence of excitatory secretory fibers in the splanchnic nerves to the fundus glands. Their data, however, are not very convincing. In Babkin's laboratory Baxter (15) proved, we believe, that the sympathetic nervous system has some relation to the secretion of mucoid fluid by the gastric mucosa. Section of the splanchnic nerves did not influence the volume of gastric secretion in response to sham feeding but the free and total acidities were lowered about eleven per cent. The output of pepsin and dissolved mucin reached its peak in the first twenty-five minutes and then abruptly fell in the splanchnotomized animals instead of gradually rising as in the normal animals. Ergotamine inhibited the "paralytic secretion" of mucoid fluid by the stomach after splanchnotomy. Bickel (16) believed that the sympathetic nerve supplies the fundic glands chiefly with inhibitory fibers. However, it has not been demonstrated definitely that the sympathetic nerves directly influence the peptic and parietal cells.

We desired to ascertain the effect of ergotamine, a sympathomimetic drug, on acid production, even though the influence of the sympathetic nervous system on the secretion of the gastric glands is not clear. Ergotamine has been found to depress and paralyze the sympathetics. It has been used clinically in migraine-like conditions, as a preliminary treatment before operations on the thyroid, and in the treatment of hyperthyroidism and "sympatheticotonia."

Fauley and Ivy (17) using Pavlov pouch dogs obtained results, showing that a definite decrease in the secretory response to a meal was obtained with a dose of ergotamine just less than the amount required to cause vomiting. Our problem was to determine the effect of ergotamine on gastric secretion in patients with duodenal ulcer. Two experiments were performed on each of 12 patients. On one day a control Ewald test-meal was given. And on another day 0.5 mgm. ergotamine tartrate (Sandoz) was injected subcutaneously twenty minutes before the Ewald meal. In most of the ergotamine experiments, the free and total acidities were moderately, but definitely lower than in the control experiments.

The average maximum free acidity in the control experiments was 55 free and 65 units of total acidity. The average maximum acidities after 0.5 mgm. ergotamine tartrate were 38 free and 45 units of total acidity. Composite curves of the acidity of twelve ulcer patients following ergotamine are compared with the control curve in Chart 1.



A moderate reduction in gastric secretion occurred with slight evidence of nausea. Six patients with duodenal ulcer were given a second dose of 0.5 mgm. ergotamine an hour after the meal. The composite curves obtained were approximately the same as though only the first dose had been given. The average values for maximum free and total acidity in the controls were 59 and 71, and after the second injection of ergotamine they were 36 and 48. When extreme nausea occurred the acidity was practically abolished.

In the histamine experiments, the patient swallowed the Rehfuss tube into the empty stomach, fasting samples were obtained, and 0.5 mgm. histamine was injected subcutaneously. Samples were withdrawn every ten minutes for two hours after the injection of histamine. A similar experiment was performed on a subsequent day except that 0.5 mgm. ergotamine tartrate was injected subcutaneously twenty minutes before the histamine injection. Table V summarizes the composite results in six patients with and without ergotamine. There is no change in the maximum free

TABLE V

Composite results in six patients using histamine as the gastric stimulus with and without ergotamine

	Vol. in 2 Hrs.	Maximum Free Acid—Cl. Units	Maximum Total Acid—Cl. Units	Total mgm. HCl
Controls (averages)	256	88	99	741
After 0.5 mgm. ergotamine (averages)	209	88	100	528

and total acidity values, but there is a slight decrease in the volume of secretion over a two hour period with a consequent reduction in the total milligrams of acid secreted.

One patient exhibited more definite diminution in acidity than the others. In one patient slightly higher acid values were obtained after ergotamine than in the control histamine test. One milligram of ergotamine tartrate decreased the response to histamine more than 0.5 mgm. did (Table VI). The larger dose not only diminished the volume of acid secreted but also decreased the height of titratable acidity.

TABLE VI

Composite results showing effect of 1 mgm. ergotamine on histamine response in six patients with duodenal ulcers

	Volume in 2 Hrs.	Maximum Free Acid	Maximum Total Acid	Total mgm. HCl
Controls (averages)	368	87	94	688
After 1 mgm. ergotamine (averages)	141	43	49	407

DISCUSSION

This investigation indicates that ergotamine tartrate in ordinary therapeutic doses definitely lowers the gastric secretory response to a meal in patients with duodenal ulcer, and in large doses diminishes the response to histamine. But, the margin between the significantly effective and harmful (nauseating) dose is too small for practical purposes. In some patients, giddiness, headache, sweating, rise of blood pressure, nausea, and vomiting may occur. In three of our patients unpleasant symptoms occurred even after 0.5 mgm. of ergotamine tartrate subcutaneously.

No evidence is presented to localize the action of ergotamine on either the nervous or humoral mechanisms of gastric secretion. The fact that one patient had higher secretion after ergotamine than in the control experiment seems to indicate that ergotamine acts only on part of the mechanism concerned in gastric secretion. The regulatory activity of the vagus nerve on gastric acid secretion is an established fact, but the influence of the splanchnics is still open to question. It is known that ergotamine, in adequate dosage, paralyzes the sympathetic. There is also some evidence (Rothlin (18)) that ergotamine may sensitize the vagus. At least it increases the susceptibility of the vagus action on the heart to electrical and chemical stimuli (acetyl choline). The vagus contains at least two kinds of excitatory secretory fibers (Vineberg (19)). One set causes a mucoid secretion and the other a juice containing acid and pepsin. Baxter (15) found both effects to be abolished by atropine, but after ergotamine there was a slight increase in the mucous secretion produced by weak rhythmic stimulation of the vagi in the neck. He attributed this slight increase to vasodilation. Could this be a sensitizing effect of ergotamine? If ergotamine sensitizes the vagus to inhibitory impulses (inhibitory nerves in the vagus for acid secretion are known to exist) transmitted to the gastric glands and thereby reduces the parietal cell secretion, atropine should abolish the ergotamine effect. Atropine and ergotamine were used in some further experiments for possible elucidation of the problem.

It has been claimed that ergotamine tartrate and atropine acted synergistically in patients with hyperacidity, and that atropine abolishes the nauseating effects of ergotamine. Experiments on dogs using histamine as the gastric stimulus show that atropine decreased the volume of secretion and ergotamine decreased the strength of the acid secreted (Table VII).

TABLE VII

Showing effect of atropine plus ergotamine on secretory response of Pavlov Pouch to histamine

	Volume	Maximum Free Acid	Maximum Total Acid	Total mgm. HCl
Average of 8 control experiments using histamine alone	23	119	133	98
Average of 8 experiments using 0.5 mgm. ergotamine and 2 mgm. atropine injected subcutaneously	6	76	95	15
Average of control experiments using 2 mgm. atropine	7	96	108	26

The atropine did not prevent vomiting, since in three experiments vomiting occurred. However, the acid secreted was no higher when vomiting did not occur.

Ergotamine 0.5 mgm. and atropine 1 mgm. were injected subcutaneously twenty minutes before 0.5 mgm. of histamine in 3 patients with duodenal ulcer. Lowering of the volume output gastric secretion, and of the total milligrams of acid secreted in a two hour period was observed, but there was no essential change in the maximum free or total acidity values (Table VIII).

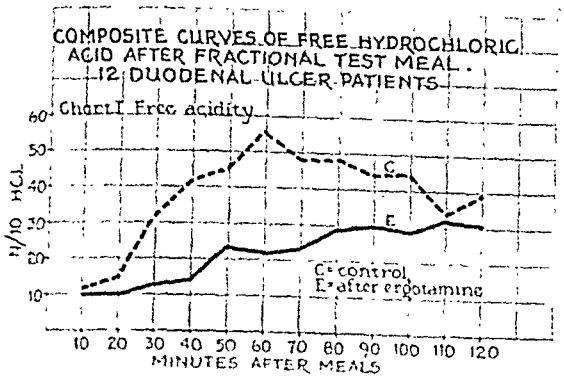
TABLE VIII

Showing combined effect of atropine and ergotamine on histamine response in three patients with duodenal ulcer

	Volume in 2 Hrs.	Maximum Free Acid	Maximum Total Acid	Total mgm. HCl
Control 0.5 mgm. histamine (averages)	254	65	70	518
Ergotamine 0.5 mgm. Atropine 1 mgm. Histamine 0.5 mgm.	132	68	70	214

Evidently atropine in the dosage used did not modify the ergotamine effect in man except to decrease further the volume and acid output.

The fact that large doses of ergotamine have some influence on the gastric response to histamine indicates that the humoral secretory regulatory mechanism may be involved, since histamine very probably acts directly on the peripheral mechanism concerned in the formation of acid. Animal experiments using Pavlov pouch dogs have been used with results more marked than those seen in our patients. More information regarding the mechanism of ergotamine action should



be obtainable by using extrinsically denervated pouch dogs and after vagotomy and splanchnotomy in dogs.

SUMMARY

1. Ergotamine tartrate in large doses diminishes the acid secretory response to histamine and to a meal.

2. The volume of secretion is usually decreased, but the peak of titratable acidity may be increased or unchanged. The summation effect is usually a diminution of the total HCl output.

3. The curve of acidity is generally depressed during the first hour after ergotamine and an Ewald meal, but may rise to normal in the second hour.

4. The margin of pharmacologic efficacy between acid inhibition and unpleasant symptoms is too narrow for this drug to be of clinical use in suppressing gastric secretion.

II.
EMETICS
APOMORPHINE

Since centrally acting emetics might influence gastric secretion either via the vagi or splanchnic nerves, we studied their effect on the gastric secretory response to histamine. Histamine was used because it is the strongest gastric stimulant known and its effects are the most difficult to diminish.

Sollman (20) states that apomorphine vomiting is prevented by very small non-narcotic doses of morphine and its esters. However, morphine alone will produce vomiting in the dog. We reasoned that if a small dose of codeine were given with apomorphine we might be able to prevent the vomiting.

One milligram of histamine, six milligrams of apomorphine hydrochloride and thirty milligrams of codeine sulphate were injected subcutaneously. The secretory response of the Pavlov pouch was diminished, but vomiting occurred (Table IX).

In man a combination of 15 mgm. of morphine sulphate and 6 mgm. apomorphine by subcutaneous injection was tried. Although the maximum free and total acidity values were unchanged the secretory curve after histamine fell much more rapidly than usual and the volume was lowered (Table X).

TABLE IX

Table showing effect of apomorphine and codeine on the secretory response of Pavlov Pouch to histamine

	Total Volume Output	Maximum Free Acid	Maximum Total Acid	Total Acid Output mgm.
Average of 6 control experiments on 2 dogs	20	119	134	98
Average of 6 experiments on 2 dogs with apomorphine and codeine	9.6	72	94	29

TABLE X

Table showing effect of morphine and apomorphine on the gastric secretory response to histamine in man

	Total Volume Output c.c.	Maximum Free Acid	Maximum Total Acid	Total HCl Output mgm.
Histamine control 2 hour response	320	64	74	520
Histamine plus 15 mgm. morphine and 6 mgm. apomorphine	134	60	72	146

APOCODEINE

Apocodeine is said to paralyze the sympathetic ganglia and to abolish the effect of splanchnic stimulation. Fifteen mgm. of apocodeine administered subcutaneously to Pavlov pouch dogs did not alter significantly the gastric secretory response to histamine.

TABLE XI

The effect of various dosages of quinine on the secretory response of the Pavlov Pouch for eight hours after a standard meal

	Total Volume Output c.c.	Maximum Free Acid	Maximum Total Acid	Total HCl Output mgm.
Average of 11 control experiments	27	76	103	80
Average when 1 gm. Quinine was given by stomach tube 1 hr. before and 1 hr. after the meal	16	72	101	38
Average with 150 mgm. Quinine injected intravenously 20 min. after the meal	19	75	104	49
Average with 300 mgm. Quinine injected intravenously 20 min. after the meal	15	74	101	40
Average with 500 mgm. Quinine injected intravenously 20 min. after the meal	14	70	98	36
600 mgm. Quinine injected intravenously 20 min. after the meal caused vomiting	11	0	11	9
1 gm. Quinine in 200 c.c. N.S.S. injected intravenously at the rate of 1 mgm. per kilo body weight per min. caused vomiting	9	0	29	8

EMETINE HYDROCHLORIDE

Emetine hydrochloride was used as another example of a centrally acting emetic, and because it is used clinically to a small extent in the treatment of peptic ulcer. Sixty-five milligrams injected intravenously in Pavlov pouch dogs decreased the acid secreted by the stomach in response to histamine by thirty per cent. One hundred and twenty milligrams stopped secretion entirely and produced vomiting and diarrhea.

QUININE

Quinine while not classed as an emetic is an example of a protoplasmic poison which when given in large doses produces vomiting by stimulating the vomiting center.

Klocman (21) reported that quinine decreased the volume of gastric secretion in dogs to about 60% of normal. He stated that the effect persisted for several days. We extended his observations by attempting to produce a complete depression of the acid secretory response of the stomach in dogs.

In the attempt to find a dosage of quinine that would be effective in inhibiting gastric secretion, but would not produce vomiting, various amounts of quinine hydrochloride were given by stomach tube and intravenously in single doses twenty minutes after a meal, and by continuous intravenous injection over a period of fifty minutes. The doses used were 150 mgm., 300 mgm., 500 mgm., 600 mgm. and 1 gm. The volume of secretion of the Pavlov pouch following a standard meal was diminished, but in order to decrease the height of titratable acidity emetic doses of 600 mgm. intravenously had to be given (Table XI).

One gram of quinine hydrochloride in 200 c.c. normal salt solution was injected at the rate of 1 mgm. per kilo weight per minute, starting the injection 20 minutes after the dog had finished a meal. This injection stopped gastric secretion, but produced vomiting.

SUMMARY

In the attempt to diminish the acid gastric secretion by the use of centrally acting emetics, we studied apomorphine, apocodeine, emetine, and quinine. With subemetic doses we were able to decrease the total acid output over the period of observation. However, in order to decrease the height of titratable acidity emetic doses had to be used. These drugs, therefore, are of no practical value in clinical use for diminishing the concentration of the acid secreted by the stomach.

We wish to express our appreciation to Miss Vivian Bass for her technical assistance.

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Influencing Factors in Nutritional Deficiency Disease

By

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NUTRITIONAL deficiency disease is due to an inadequate supply, absorption or utilization of vitamins, mineral salts or nutritional factors normally formed in the body from food elements. It has long been known that certain "deficiency diseases" such as scurvy and beri-beri result from an inadequate supply of certain vitamins. Only recently have we realized that a lack of necessary nutritional factors may play an important part in producing symptoms in many different diseases or may explain symptoms for which there has hitherto been no adequate explanation. Thus Mackie (1) has emphasized the great importance of nutritional deficiency disease in chronic ulcerative colitis, and Weiss (2) in the production of cardiac symptoms when the supply of vitamin B is inadequate.

Deficiency disease is due to the non-use of a specific nutritional factor at the site in the body where it is needed and normally utilized. The factor manifested cannot be used if it is not present, but it may be present, and yet not be utilized. The actual incorporation of a nutritional element necessitates an adequate supply, adequately absorbed and adequately utilized.

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For example, to prevent the development of pernicious anemia the bone marrow must constantly be supplied with the erythrocyte maturing factor formed normally in the stomach by the interaction of the intrinsic factor secreted by the gastric glands on the extrinsic factor taken in with the food. In idiopathic pernicious anemia there is a defect in supply since the stomach does not form the intrinsic factor; in sprue the factor is formed but lost on account of diarrhea; in myxedema, it may reach the marrow and not be used. In each of these three conditions the bone marrow may show the same response, namely the production of a macrocytic anemia.

In every patient with deficiency disease we must evaluate the factors influencing the supply, absorption and utilization of the specific nutritional elements. The more important factors to be considered are:

1. The normal reserve supply in the body.
2. The amount ingested or lost by vomiting or diarrhea.
3. The needs of the body especially as influenced by pregnancy, lactation and hypermetabolism.
4. Impairment of absorption from the gastro-intestinal tract by:
   a. achlorhydria
   b. hypometabolism
   c. toxemia
   d. circulatory insufficiency
   e. presence of certain substances such as mineral oil
5. Impairment of utilization in tissues by:
   a. toxemia as from chronic nephritis or infection
   b. metallic poisons as lead
   c. hypometabolism
   d. imbalance of food especially an excessive intake of carbohydrate
   e. imbalance of specific nutritional factors

It is apparent that the amount of any nutritional element available for use at any time is much influenced by the normal reserve level. The reserve of vitamins B, C and D and iron is very limited, while the body has the power of adequately storing vitamin A, most of the mineral salts, and the erythrocyte maturing factor protective against pernicious anemia. This fact partly explains the more frequent occurrence of some deficiencies than others.

All nutritional factors must be taken in as food or medication or formed in the body from food, hence the supply is directly related to the intake. Certain elements such as vitamin B and iron are normally present in most foods only in small amounts. Long continued vomiting or diarrhea will cause a deficiency even if the nutritional elements are ingested in abundance since absorption is interfered with. Patients who regularly take only small amounts of food not infrequently have a deficient quantitative intake although the diet may be qualitatively adequate. A combination of small intake and some vomiting, such as occurs in the early part of almost every pregnancy, is a potent factor in causing deficiency disease in pregnancy.

The amount of food which is adequate under normal conditions may be inadequate under conditions requiring larger amounts than normal. Pregnancy and lactation are the two physiological states requiring more nutritional elements. Hypermetabolism from any cause increases the need since the level of chemical activity is here much higher. The more important clinical causes are fever, leukemia, and hyperthyroidism.

Numerous factors may interfere with absorption after the nutritional elements are taken into the gastro-intestinal tract. The presence of achlorhydria has a definite effect on the efficiency of absorption, especially of the mineral elements. The iron deficiency anemias are much more common if free hydrochloric acid is absent from the gastric contents. This may be a chemical problem secondary to insufficient solution of iron in the absence of hydrochloric acid or may possibly be due to the lack of some factor necessary for the metabolism of iron whose absence is indicated by the achlorhydria, just as the achlorhydria of pernicious anemia is of importance only as indicating the absence of the intrinsic factor of Castle.

Hypometabolism necessarily interferes with absorption since here the level of vital activity is decreased. In most instances of hypometabolism, the metabolic level is probably not sufficiently lowered to make much difference alone but in myxedema where the basal metabolic rate is 30 to 40 per cent below normal, such a lowering of chemical activity is very important. A mild hypothyroidism may be important also when added to other factors.

A toxemia from any cause may interfere with absorption although this is probably much more important in affecting utilization than absorption. Circulatory insufficiency necessarily impairs absorption. The chronic and excessive use of mineral oil may impair the absorption of the vitamins. This has already been discussed in relation to vitamin A (3) and, from clinical observations, I am more and more impressed with the probability that mineral oil may also interfere with the absorption of vitamin B.

It is increasingly evident to students of nutritional disease that impaired utilization of specific factors in the tissues where they are necessary frequently precipitates the symptoms of deficiency disease. In such cases there is little therapeutic effect from giving more of the missing factors. A toxemia from chronic nephritis or an infection may act in such a manner. Metallic poisons, especially lead, produce a hypochromic or iron deficiency anemia which is not influenced by iron therapy. It is very probable that the neuritis of lead poisoning is due to a deficiency of vitamin B rather than a direct toxic effect of lead on the nerves. The lead here interferes with the utilization of both iron and vitamin B. This fact explains the ineffectiveness of iron or vitamin B in lead poisoning since the fault is in utilization and not in supply.

Hypometabolism will interfere with utilization just as it does with absorption due to a lowering of the level of chemical activity. It has long been observed clinically that iron may have no effect in an iron deficiency anemia unless given with thyroid extract. In such cases the utilization of iron is probably impaired by the hypometabolism.

A food imbalance may also influence the utilization of nutritional factors. An excess of carbohydrate especially will interfere with the use of vitamin B. This may be due to the fact that vitamin B is necessary for the oxidation of carbohydrates, so far unproved, or that some balance between carbohydrate and vitamin B is necessary as emphasized by Cowgill (4). Mc-

Carrison (5) showed long ago that a vitamin B deficiency will develop in a monkey in normal nutritional balance if carbohydrate alone is added to the diet. Little is known about the effect of an imbalance of other food elements on the utilization of specific nutritional factors.

It is quite probable that some balance between the specific nutritional elements may be necessary also. Certain types of nutritional deficiency constantly occur together. This is best illustrated by the frequent finding of an iron and vitamin B deficiency together. It seems probable here that iron influences the utilization of vitamin B or vice versa.

DISCUSSION

I have outlined the manner in which the development of nutritional deficiency disease may be influenced. Whenever deficiency disease is considered as a possible factor in a patient's symptoms the absorption and use of nutritional elements as well as the supply must be evaluated.

This discussion only emphasizes the many possible conditioning factors. These must be identified if possible since the treatment of deficiency disease, when due to deficient absorption or utilization, is a problem in treating the influencing factor rather than in supplying more of the missing element. Fortunately, at times providing an excessive supply of the factor needed may overcome a defect in absorption or utilization which cannot be treated or removed.

Every true deficiency disease is a chemical problem in which all possible influencing factors in the development of the disease must be considered. It is especially necessary to recognize the importance of the summation of several conditioning factors.

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Clinical and Pathological Manifestations of Carcinoma of the Stomach

By

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DURING the past seven years, one hundred thirty-two cases of carcinoma of the stomach have been studied on the gastro-intestinal service of the Buffalo City Hospital. We will review this series of cases and endeavor to evaluate and compare the important factors manifested, with some of the current medical literature on this subject.

AGE AND SEX INCIDENCE

Carcinoma of the stomach is usually considered a disease of middle age. In a series of five hundred forty-one cases, reported by Minnes and Geschicter, seventy-eight per cent occurred between the ages of forty-four and sixty-six years, ten per cent before the age of forty and two and six-tenths per cent after the age of seventy. The youngest in their series was twenty-five and the oldest eighty. In our series, the youngest was twenty years of age, while the oldest was eighty-one. The highest percentage, seventy-seven and three-tenths, occurred between the ages of forty and seventy.

Walton reviewed six hundred fifty cases and found that one hundred fifty occurred between the ages of fifty-one and sixty. Five of his cases occurred before the age of thirty, while in our series three cases or three and two-tenths per cent occurred before the age of thirty.

Minnes and Geschickter found gastric cancer to be three times as common in males as in females, while the Mayo Clinic shows the ratio to be slightly higher. In our group there were one hundred nine males, eighty-two and six-tenths per cent, and twenty-three females, seventeen and four-tenths per cent, approximately five times as common in the male as in the female.

The disease occurred in one hundred twenty-five members of the white race and seven members of the colored race. While our cases on the service are predominatingly white, still the incidence in the white race is much greater than in the colored race.

Age Incidence	No. of Cases	Percentage
20-30 years of age	3	2.2%
31-40 years of age	7	5.3%
41-50 years of age	26	19.7%
51-60 years of age	33	25.0%
61-70 years of age	43	32.6%
71-80 years of age	18	13.6%
Over 81 years of age	2	1.5%
	132	99.9%

SYMPTOMATOLOGY

In our series of one hundred thirty-two cases, the outstanding complaint was epigastric pain, present in more than seventy per cent of the cases. Flatulence and anorexia occurred in fifty-eight per cent of cases. Emesis was complained of in sixty-nine per cent. In only a small group of ten cases was hematemasis present. Enlargement of the abdomen occurred in five

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and three-tenths per cent. It is therefore evident that there are no pathognomonic symptoms which would permit the early recognition of the disease. Minnes and Geschickter in their series of over five hundred

Incidence by age and sex of carcinoma of stomach

Observer	No. of Cases	Average Age	Percentage	
			Males	Females
Minnes and Geschickter	541	53.6		
Mason	1912	53.7	78.8%	21.2%
Balfour-Harris	1000	54.	79. %	21. %
Walton	650	57.2		
Levitt and Argue	132	57.5	82.6%	17.4%

cases found the most constant and conspicuous feature was the rapid loss of weight, observed in ninety-one per cent of their cases, and which corresponds closely with the findings in our group. Epigastric pain was present in seventy-four and eight-tenths per cent in their series.

PREVIOUS HISTORY

In one hundred twenty-one cases of the group studied, the duration of gastro-intestinal symptoms varied between one month and ten years. Thirteen patients had symptoms referable to the stomach less than one month before the diagnosis was established. The majority had complaints between five and twelve months. In fifteen cases, eleven and three-tenths per cent, a diagnosis of gastric ulcer had been made before it was established that carcinomatous changes were present.

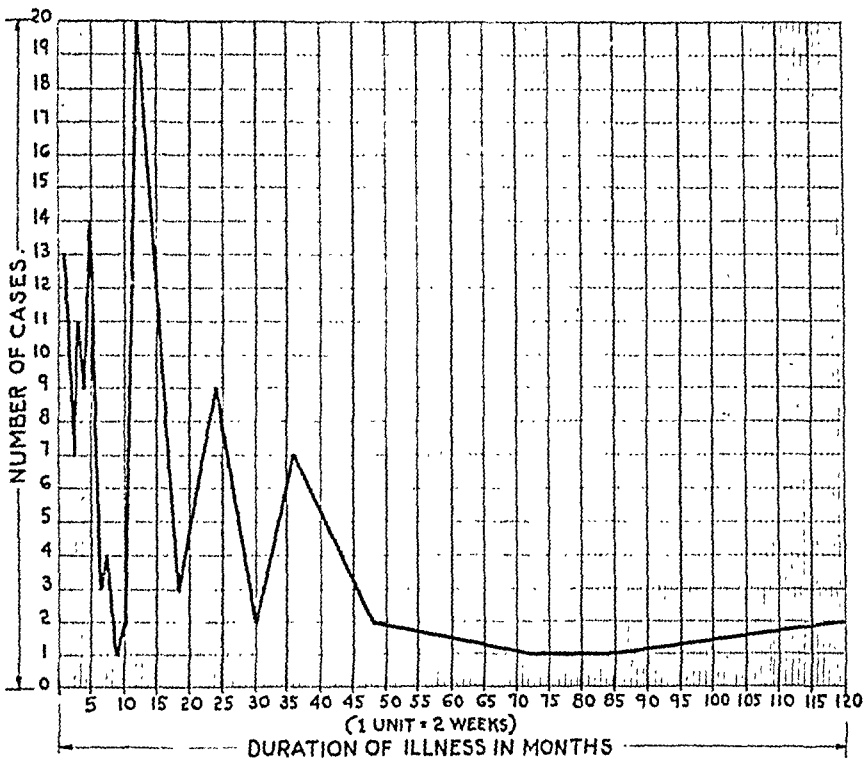
PHYSICAL SIGNS

Physical examination in the early stages of the disease may reveal very little. The presence of a palpable mass in the epigastrium signifies the advanced stage of carcinoma. It was found in forty-three and six-tenths per cent of the cases studied by Minnes and in

Symptoms

Loss of weight	115 cases	87.1%
Epigastric pain	95 cases	71.9%
Emesis	92 cases	69.6%
Flatulance and anorexia	77 cases	58.3%
Constipation	48 cases	36.3%
Weakness	34 cases	25.7%
Tarry stools	25 cases	19. %
Lower abdominal pain	9 cases	6.8%
R.U.Q. pain	8 cases	6. %
Enlargement of abdomen	7 cases	5.3%
Diarrhea	3 cases	2. %
Dysphagia	3 cases	2. %
Jaundice	2 cases	1.5%
L.U.Q. pain	1 case	.7%

forty-four and six-tenths per cent in our series. Epigastric tenderness was observed in his group in thirty-two and three-tenths per cent, and in thirty-three and three-tenths per cent in our series. Emaciation was the outstanding clinical manifestation present in our series and was observed in sixty-two and eight-tenths per cent of the group. It is interesting to note that Virchow's node was present only four times in the



Physical signs

Emaciation	83 cases	62.8%
Epigastric mass	59 cases	44.6%
Epigastric tenderness	44 cases	33.3%
Enlargement of liver	36 cases	27.2%
Pallor	22 cases	16.6%
L.U.Q. mass	15 cases	11.3%
Abdominal distension	13 cases	9.8%
R.U.Q. mass	11 cases	8.3%
Jaundice	8 cases	6.0%
Ascites	5 cases	3.7%
Abdominal spasm	4 cases	3. %
Virchow's node	4 cases	3. %
Invisible peristalsis	3 cases	2. %
Prominent abdominal veins	2 cases	1.5%
R.L.Q. mass	2 cases	1.5%
L.L.Q. mass	2 cases	1.5%
Rectal mass	1 case	.7%
Large cervical glands	1 case	.7%
Smooth tongue	1 case	.7%

entire series. Hepatic enlargement was observed in thirty-six patients and ascites in only five of this group.

LABORATORY WORK

The absence of free hydrochloric acid in the gastric contents has long been regarded as a constant finding in carcinoma of the stomach. In a series of three hundred thirty-nine cases studied by Hartman, achlorhydria was observed in sixty-four and six-tenths per cent of the group, hypo-chlorhydria in twenty-five and nine-tenths per cent and normal values in six and seven-tenths per cent of cases. In our series, eighty-one per cent showed absence of free hydrochloric acid. The remainder showed varying degrees of hydrochloric acid present. Occult blood was present in both gastric contents and the stool of all cases. The blood Wasserman was positive in only seven cases of the entire group.

Roentgenographic studies of the gastro-intestinal tract were made in ninety-three cases. Of this group the diagnosis of carcinoma was made in eighty-one and seven-tenths per cent, ulcer of the stomach in five and three-tenths per cent, while the remainder of the group were reported as negative. Obstruction as evidenced by retention of the barium meal was observed in thirty cases. Since the entire group had carcinoma of the stomach, the X-ray diagnosis was conclusive in the majority of cases.

Blood examinations were made in ninety cases of the group. The hemoglobin was under sixty per cent in thirty-eight cases and eighty per cent or less in seventy-four cases. The red cell count was under three million in twenty cases and under four million in sixty-three cases, suggesting that a hypochromic anemia was predominant. In seventy cases a leukocytosis above eight thousand was present.

LOCATION OF CARCINOMA

In tabulating the location of the cancer in the stomach we include the findings of X-ray, autopsy and surgery. This gives us one hundred forty-two lesions observed in our series of one hundred thirty-two cases.

Location of carcinoma

Pylorus	79 cases	55.6%
Lesser curvature	13 cases	9.1%
Pars cardia	11 cases	7.7%
Pars media	7 cases	4.9%
Entire stomach	1 cases	2.8%
Greater curvature	4 cases	2.8%
Duodenum	1 case	.7%
Pre-pylorus	1 case	.7%
Undetermined	22 cases	15.5%

RESULTS

Forty-four cases of our entire series were submitted to surgery. In sixteen of this group, a laparotomy was performed, and the lesion was considered far advanced. In twenty-two cases a gastro-enterostomy was performed. A gastric resection was done in six cases. Of the total group operated upon, four cases lived for one year following the operation, the remaining number died within a period of less than one year.

Thirty-six cases of our series were autopsied and the diagnosis of carcinoma of the stomach was confirmed. In the autopsied group twelve cases showed metastases to the regional lymph nodes, and a similar number showed metastases to the liver. Five cases showed involvement of the omentum, four of the peritoneum, and two each in the pleura and spleen. The esophagus, mediastinum, brain, pancreas and renal vein were each found to be involved once in separate cases. Ten cases showed no metastatic involvement. Associated findings in the autopsied group were cholelithiasis, cirrhosis of the liver, diverticulosis of the colon and gastric ulcer once each in separate cases.

COMMENTS

Dr. Allen A. Jones. The examination of gastric contents for the presence of lactic acid, macroscopic, microscopic or occult blood and Oppler-Beas bacilli is of great importance in gastric carcinoma. Usually, in the presence of lactic acid, hypochlorhydria or achlorhydria is found but, in some instances, free hydrochloric acid is present with a definite positive chemical test for lactic acid. It is best to examine the morning fasting stomach contents using the fractional method.

Even gastroscopy or X-ray may fail to reveal a malignant process in the stomach.

In the presence of more or less epigastric pain, anorexia, steady and rather rapid loss of weight and a markedly increased sedimentation rate of the red blood cells, malignancy should be suspected.

The authors wish to express their appreciation to Dr. George B. Pantera for assistance in compiling the statistics.

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The Value of Diagnostic Non-Surgical Biliary Drainage as Compared with Cholecystography*

(An Analysis of Biliary Drainage Findings in 64 Operated Cases Compared with Findings by Cholecystography in 60 of These Cases)

By

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and

LESTER C. B. SPIER, M.D.

NON-SURGICAL biliary drainage has now been in use for nearly two decades. However, it has not received as universal an acceptance as has cholecystography. In the hands of many workers, the value of biliary drainage compares favorably with that of cholecystography in the diagnosis of biliary tract pathology, particularly cholelithiasis. Bockus (1) showed that the cholecystogram demonstrated stones in 29.2% while biliary drainage suggested the presence of stones in 83.2% of 148 proved stone cases. In 79 stone cases where the gall bladder was still functioning, 97% showed crystals in the preoperative bile. Cholecystography demonstrated pathology in 88.4%, while drainage showed pathology in 98% of 143 proved stone cases. From this clinic four years ago Doran, Lewis, Denneen and Hanssen (2) published a paper enthusiastically endorsing biliary drainage as a diagnostic procedure. We are still employing it routinely in all cases attending the gall bladder clinic.

Rousselot (3) in 1933, described a technique of drainage which was invariably successful. By using a tube with a metal stilet, he was able with the assistance of a fluoroscope to pass the tube into the duodenum in a very short time. He found biliary drainage valuable in the diagnosis of cholelithiasis.

In our clinic we have found that with a Twiss (4) duodenal tube, unsuccessful drainages are much less common than with other types. If a drainage is unsuccessful, it is repeated the following week, the patient in the meantime taking 10 minims of Tincture of Belladonna three times daily following meals. This usually succeeds in overcoming the pylorospasm. Twenty-five per cent magnesium sulphate and olive oil are used as stimulants. Very often we obtain concentrated bile after stimulation with olive oil when the magnesium sulphate stimulation has failed. Rarely do we fail to obtain concentrated bile from a gall bladder which functions normally by cholecystography.

The bile is examined macroscopically for color. A dark olive-green or molasses color usually denotes good gall bladder function. If no concentrated bile is obtained we conclude that the gall bladder is not functioning. The sediment is inspected. The presence of brick-red particles is usually due to the presence of calcium bilirubinate pigment. The bile sediment is examined microscopically for cholesterol crystals, calcium bilirubinate pigment, and bile-stained pus cells. Cholesterol crystals are easily recognized as colorless, rectangular crystals with a corner punched out. Calcium bilirubinate pigment appears as lustrous orange or gold-colored granules; less often it appears as brick-red particles.

Preoperative non-surgical biliary drainages were done in 64 operated cases (See Table). Crystals were found in the bile in 27 cases or 43.5%. At operation stones were present in 22 of the 27, or 81%. Of these 27 cases, calcium bilirubinate pigment without cholesterol crystals was present in 10. At operation stones were present in 9 of the 10 cases, or 90%. Cholesterol crystals alone were present in 11. In 10 of these, stones were present at operation, or 91%. Both cholesterol crystals and calcium bilirubinate pigment were present in 6 cases. Stones were found at operation in 3, or 50%.

Of the 62 cases studied, 48 had stones at operation. Of these 48 cases, 21 had crystals in the preoperative bile, or 43.7%; 19 showed neither crystals nor concentrated bile. Pathological drainage findings, that is, the presence of crystals or the absence of concentrated bile, were found in 40 of the 48 stone cases, or 83.3%. The remaining 8 patients with stones, or 16.6%, had a normal biliary drainage.

In 5 of the 14 patients, 35.7%, with a pathological gall bladder without stones at operation, crystals were present in the preoperative bile obtained by biliary drainage.

SUMMARY

1. An analysis of biliary drainage findings in 62 operated cases is presented.

2. In 83.3% of cases showing cholelithiasis at operation the preoperative biliary drainage findings were suggestive of gall bladder pathology.

3. In 43.7% of cases showing cholelithiasis at operation, the diagnosis was suggested by the presence of crystals in the bile obtained by biliary drainage prior to operation.

4. 81% of the patients suspected of having gall bladder disease and showing crystals in the bile had stones at operation.

5. Approximately one-third of the patients who at operation had a diseased gall bladder without stones had crystals in the preoperative bile.

CHOLECYSTOGRAPHY

Cholecystograms were done in 60 of the above mentioned operated cases. 31 showed failure of visualization, 15 showed shadows suggestive of calculi, 6 were reported as faint visualization, 1 showed normal visualization with delayed emptying, and 7 revealed normal visualization and normal emptying.

*From the Gall Bladder Clinic—Fourth Surgical Division, Bellevue Hospital.

Analysis of 64 consecutive operated cases with pre-operative biliary drainage and roentgenological findings

	Concentrated Bile	Macroscopical Findings	X-ray With Dye	Findings at Operation			Other Pathology
				Calculi			
				Gall Bladder	Cystic Duct	Common Duct	
1. P. L.	—	Negative	NVNE*	—			Atrophic gall bladder
2. M. P.	0	Cholesterol	OV*	+	—		Atrophic gall bladder
3. R. M.	0	Negative	OV	+			Atrophic gall bladder
4. M. M.	+	Bilirubin Ca	NVNE	+			Chronic cholecystitis
5. C. B.	0	Bilirubin Ca	NV Calculi	+	+		Chronic productive cholecystitis
6. R. H.	+	Cholesterol	NVDE*	+			Cholecystitis Atrophic gall bladder
7. F. S.	0	Negative	FVNE*	+			Atrophic gall bladder
8. D. B.	0	Bilirubin Ca	OV	+			Atrophic gall bladder
9. S. S.	0	Negative	OV	+			Atrophic gall bladder
10. J. D.	0	Negative	OV	+			Chronic productive cholecystitis
11. F. D.	0	Negative	OV	+	+		Empyema of gall bladder (cholecystostomy)
12. F. E.	0	Cholesterol	OV	+	+		Atrophic gall bladder
13. P. L.	+	Negative	NVNE	+			Atrophic gall bladder
14. A. H.	0	Negative	OV	+			Chronic productive cholecystitis
15. J. B.	0	Negative	Calculi	+			Acute exudative cholecystitis
16. L. P.	0	Negative	OV	+	+		Atrophic gall bladder
17. E. C.	—	Cholesterol	NVNE	+			Atrophic gall bladder
18. J. M.	0	Negative	OV	+			Acute suppurative cholecystitis
19. J. M.	+	Negative		+			Atrophic gall bladder
20. M. G	+	Cholesterol Bilirubin Ca	NV Calculi	+			Fibrosed gall bladder
21. A. M.	—	Cholesterol	NVNE Calculi	+			Chronic cholecystitis
22. E. S.	+	Bilirubin Ca	NVNE Calculi	+			
23. G. V.	0	Negative	FV	+			Acute and chronic cholecystitis
24. M. C.	0	Cholesterol Bilirubin Ca	OV	+			Chronic cholecystitis
25. R. F.	+	Negative	Calculi	+			Sclerosed gall bladder
26. J. I.	0	Bilirubin Ca	NVDE Calculi	+	+		Atrophic strawberry gall bladder
27. E. B.	0	Cholesterol	FV Calculi	—			Atrophic gall bladder
28. J. B.	+	Negative	OV Calculi	+			Atrophic gall bladder
29. J. G.	0	Negative	OV	+			
30. A. D.			FV Calculi	+			Sclerosed gall bladder
31. L. Z.	+	Negative	OV	+			Chronic cholecystitis
32. I. L.	0	Negative	OV	+			Cholesterosis
33. L. G.	0	Negative	OV	+			Chronic cholecystitis
34. A. M.	0	Negative	OV	+			
35. A. S.	+	Bilirubin Ca	NVDE Calculi	+			Atrophic gall bladder
36. I. D.	+	Bilirubin Ca	OV Calculi	+	+		Chronic productive cholecystitis
37. F. G.	0	Cholesterol Bilirubin Ca	NV	0			Atrophic gall bladder
38. A. S.	+	Cholesterol	OV	0			Atrophic gall bladder
39. B. P.	0	Negative		0			Contracted gall bladder
40. S. S.	+	Negative	NVNE	0			Chronic productive cholecystitis
41. A. S.	+	Negative		0			Acute exudative cholecystitis Atrophic gall bladder
42. L. S.	0	Cholesterol Bilirubin Ca	OV	0			Chronic cholecystitis
43. N. G.	+	Cholesterol Bilirubin Ca	OV	0			Atrophic gall bladder
44. C. G.	+	Negative	OV	0			Empyema of gall bladder (cholecystostomy)
45. A. K.	+	Negative	OV	0			Atrophic appendix, and hyperplasia gall bladder mucous membrane
46. K. R.	0	Negative	OV	0			Chronic productive cholecystitis
47. R. J.	0	Negative	FV Calculi	0			Subacute cholecystitis
48. H. C.	0	Negative	NVNE	0			Atrophic gall bladder
49. J. G.	0	Negative	OV	0			Sclerosed gall bladder
50. D. E.	+	Cholesterol	OV	+			Fibrosed gall bladder
51. N. S.	0	Bilirubin Ca	NVNE Calculi	+			Atrophic gall bladder
52. M. V.	+	Negative	OV	+			Chronic cholecystitis wall six times normal thickness
53. F. D.	0	Negative		+			Chronic productive cholecystitis
54. S. M.	+	Cholesterol	OV	+		+	Chronic productive cholecystitis
55. L. D.	0	Bilirubin Ca	FV Calculi	—			Chronic cholecystitis B. coli—in bile and G. B. wall
56. J. S.	+	Negative	OV	—			Chronic cholecystitis
57. L. D.	—	Cholesterol	FV	—			Chronic cholecystitis
58. E. B.	0	Negative	FV	+			Chronic cholecystitis
59. A. W.	0	Cholesterol	FV	—			Chronic cholecystitis
60. B. S.	0	Negative	FV	—			Chronic cholecystitis
61. A. C.	0	Bilirubin Ca	OV	0			Chronic cholecystitis
62. A. C.			OV	—			Chronic cholecystitis
63. M. L.	0	Cholesterol Bilirubin Ca	OV	—			Chronic cholecystitis
64. J. R.	0	Negative	OV	—	—		Dilated thickened gall bladder

OV—No visualization of gall bladder.
NV—Normal visualization of gall bladder.
FV—Faint visualization.

DE—Delayed emptying
Calculi—Shadows resembling calculi seen in roentgenogram.

Of the 31 cases showing failure of visualization, stones were present in 23, or 74.2%. The 8 remaining cases showed various types of gall bladder pathology such as fibrosis or atrophy, chronic cholecystitis, and empyema. Of the 15 cases in which shadows suggestive of calculi were reported, stones were present at operation in 13, or 93.3%. In the 6 cases showing faint visualization by cholecystography, stones were found at operation in every case (100%). Of the 7 cases showing a normal cholecystogram, 3 showed stones at operation (43%). In the one case showing normal visualization and delayed emptying, stones were present at operation.

In 46 proved stone cases, the cholecystographic findings were as follows: 14, or 30%, shadows suggestive of calculi; 50%, no visualization; 13%, faint visualization; and 6.7% normal visualization and normal emptying.

SUMMARY OF CHOLECYSTOGRAPHIC FINDINGS

1. An analysis of cholecystographic findings in 60 operated cases is presented.

2. While only 30% of gall stone cases coming to operation showed stones by cholecystography, over 93% showed a pathological cholecystogram, viz. calculi, no visualization, faint visualization or normal visualization with delayed emptying.

3. In patients suspected of having gall bladder disease a pathological cholecystogram almost invariably indicates a pathological gall bladder. If the cholecystogram is reported normal there is a larger error; 6.7% of stone cases and 20% of other types of gall bladder pathology failed to show a pathological cholecystogram.

COMPARISON OF DIAGNOSTIC VALUE OF CHOLECYSTOGRAPHY WITH THAT OF BILIARY DRAINAGE

In patients with cholelithiasis, cholecystography was superior in revealing pathology — 93% as compared with 83.6% for biliary drainage. Actual calculi were demonstrated in cholecystograms in 30% of cases while the presence of calculi was suggested by biliary drainage in 43.7%. When findings by biliary drainage and by cholecystography are both considered, pathology was indicated in 95.9%.

CONCLUSIONS

1. Non-surgical biliary drainage is a useful diagnostic procedure.

2. It compares favorably with X-ray in the diagnosis of biliary tract pathology.

3. Finding crystals in the bile is not pathonomonic of stones, but is evidence of pathology in the biliary tract.

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Abstracts

HENRY KENDALL MULFORD

America lost one of its foremost exponents of preventive medicine in the passing of Henry Kendall Mulford, in his 71st year, on October 15, 1937.

The company which bore Mr. Mulford's name was the first in this country to commercially distribute antitoxins. Small Pox Vaccine and curative serums used in the prevention and cure of infectious and contagious diseases were soon added. Through the distribution of these biologicals, he was probably responsible for the saving of more lives than any other man in the history of medicine and pharmacy. These alone stand as a fitting monument to his life of service to humanity, and thanks to his stimulating influence on the younger men whom he drew around him, the good work that he accomplished and new work started will continue to grow on and on.

The story of the life of Mr. Mulford, as unfolded by men who have known him since his embarkation into the field of pharmacy, is of interest. Born in Bridgeton, New Jersey, October 10, 1866, of old New England stock, H. K. (Henry Kendall) Mulford came from a family of sea captains, and his forebears played an important part in local history. He attended the Bridgeton elementary school, later the South Jersey Institute, a military prep school having a curriculum comparable with present college work.

A Fitting Background

Starting his drug career at the age of 18 in the employ of Dodge & Olcott, New York, appreciating at this early period the need for a sound basis on which to begin his life's work, he returned to Philadelphia. He secured a job (not a position) in the drug store at 18th and Market Streets, Philadelphia, operated by the later world-wide known teachers, Dr. Joseph P. Remington and Dr. L. E. Sayre. Everyone in medicine and pharmacy knows the history of Drs. Remington and Sayre, and this first employment in a retail drug store furnished a fitting background for the future that Mr. Mulford made for himself.

When Dr. Remington decided to devote his full time to the Philadelphia College of Pharmacy, and U.S.P. work, he disposed of his interest in the retail store to Dr. Sayre. Within a few months Dr. Sayre was elected as Dean of the College of Pharmacy of the University of Kansas, and he sold one-half interest to Mr. Mulford, who having previously qualified as proprietor by passing the state board, was in charge of the business.

In the interim, Mr. Mulford took the pharmacy course at the Philadelphia College of Pharmacy, and after waiting a year on account of age requirements, for his sheep-skin, at the age of 21 he became a full-fledged pharmacist, and the complete owner of this drug store.

It is significant that Mr. Mulford's predecessors were leaders in pharmacy.

In the Pharmacy (now nearly 160 years old) in which Mr. Mulford started his actual pharmaceutical experience, Henry Bowers made glycerine; Samuel Eastbrook perfected medicated lozenges; Drs. Remington and Sayre developed their background and Mr. Mulford started his work on the standardizing of drugs and later began his research in the biological field. Mr. Mulford was the first in this country to supply Diphtheria Antitoxin for use by the medical profession distributed through the pharmacist.

As an ethical pharmacist, besides making his own U.S.P. and N.F. prep-

ations, being of an originative type, Mr. Mulford began perfecting and manufacturing various pharmaceutical specialties, and in 1890 he formed the firm bearing his name, The H. K. Mulford Company, and manufactured for distribution through the wholesale and retail drug trade, a line of pharmaceuticals, featuring compressed tablets, for the manufacture of which he perfected and patented the well-known Crown Tablet machine.

Associated with Mr. Mulford at the outset of this company was Dr. E. V. Pechin, a graduate of the Philadelphia College of Pharmacy, and now retired.

His Biological Work

In 1893, Mr. Mulford began studies in the production of Diphtheria Antitoxin, and always associated with him the leaders in bacteriologic, immunological and bio-chemical research work.

The progress in biological history during the period from 1893 to the time of his death is emblematical of the foresight of Mr. Mulford. Success was largely due to his dynamic energy combined with his dominant characteristics of ethics in pharmaceutical manufacturing, perserverance, and his love of fellowman, which not only influenced the direction of his associates, but secured active cooperation of his coworkers; he believed in giving authority with responsibility.

A Leader in Colloid Therapy

Realizing the principle that life itself is the application of the colloidal equation, in 1921 Mr. Mulford directed his study to Colloid Chemistry and later established the Mulford Colloid Laboratories. His work in this field has been successful in the production of medicinal colloids (Sulphur, Manganese, Iron and Iodine, etc.) and in developing antigens for the treatment of poison ivy.

In 1926, he accepted the Directorship of Research and Biological Laboratories of The National Drug Company at 5109 Germantown Avenue, Philadelphia, and at the biological laboratories at Swiftwater, Pa., Mr. Mulford actively worked in developing biological products for the interests of humanity, and in striving to protect and save human lives.

Ethical to the nth degree, Mr. Mulford believed in the highest standards of manufacture of biological products, and in their distribution through the ethical pharmacist by selective distribution. He was a leader in biological and galenical standardization. In addition to having established the first biological laboratory in the U. S. for the production of Diphtheria Antitoxin, Mr. Mulford was one of the first advocates of the development of the standardization of biologicals and galenicals. In work, he had the active cooperation of Dr. Edgar Fahs Smith, late Dean of the University of Pennsylvania, Dr. George H. Meeker, now Dean of the Post-Graduate School of Medicine of the University of Pennsylvania, the late Dr. A. C. Abbott, Prof. of Bacteriology and Director of Hygiene, University of Pennsylvania Medical School, and his assistant, the late Dr. David H. Bergey, who succeeded Dr. Abbott as professor and director. Dr. Bergey was the first scientist of this country to test antitoxins for potency according to the Ehrlich standards. It was significant that after a 40 year friendship, Dr. Bergey became an associate with Mr. Mulford as the Director of Research in Biology for The National Drug Company, up to the time of Dr. Bergey's death.

Widely Honored

The degree of Master of Science was conferred upon Mr. Mulford by Lafayette College in 1918, and the highest honor in pharmacy, Master of Pharmacy, was conferred upon him by his Alma Mater, the Philadelphia College of Pharmacy and Science, in 1933. He was a member of the American Pharmaceutical Association, American Drug Manufacturers Association, American Pharmaceutical Manufacturers Association, American Chemical Society, the Franklin Institute and the Union League.

Mr. Mulford was active right up to the last. A week before his death, he attended the American Public Health Association meeting in New York, and the Pennsylvania State Medical Society meeting in Philadelphia.

The drug world, educators and publishers deeply mourn the death of H. K. Mulford, an inspirational leader; an indefatigable worker; a man among men; unimpeachable in character and integrity, a loving husband, father and grandfather, a man loved and beloved by all who knew him, and his friends were legion.

Our sympathy is sincerely extended to his widow, Mrs. Lillian Ware Mulford; a daughter, Mrs. H. H. Fehr; a son, H. K. Mulford, Jr. and a brother, Lewis J. Mulford of New York, who survive him.

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*Jeghers, H.

The Degree and Prevalence of Vitamin A Deficiency in Adults. J. A. M. A., 109:756, Sept. 4, 1937.

Out of 162 students tested on the biophotometer for evidences of vitamin A deficiency, 50 were selected as showing the best dark adaptation, another 50 were chosen as subnormal, and nutritional, clinical, and other data were compiled for both groups. Of the entire 162, 35 per cent had low photometer readings, and 12 per cent had clinical manifestations of the deficiency.

Although the incidence of colds was about the same in both groups, the duration and severity of colds was less in the normal group than in the subnormal. About half of the latter group had definite night blindness, and 15 had dryness of the skin.

The vitamin A deficiency was treated by giving 70,000 units of vitamin A in the form of carotene orally for two weeks, followed by 25,000 units daily until dark adaptation became normal. Therapeutic results were striking, 36 cases having regained normalcy, and 9 being improved.

Estimates of the necessary minimum vitamin A intake vary from 1000 to 8700 units daily, but the author found that all persons who consumed over 4000 international units daily were normal. He suggests, however, that 50 per cent over this figure be allowed for optimal benefits. Individuals vary in capacity to absorb, store, convert, and destroy vitamin A.

Among foods yielding liberal amounts of vitamin A are milk, butter, cheese, cream, eggs, liver, spinach, carrots and most green and yellow vegetables, fish roe, prunes and kidneys. Poor choice of foods was mainly responsible for the vitamin deficiencies found.

Jeans, P. C. and Stearns, G.

The Vitamin D Requirement of the Child. Am. J. Dis. Childr., 54:189, July, 1937.

In the first year of life, retention of calcium increases with calcium intake if vitamin D is given, but not without vitamin D. When milk with 135 units of vitamin D to the quart is fed at the level of 1.8 ounces (53 c.c.) to the pound (0.45 Kg.) of body weight, most infants show more than the calculated minimum retention, but with smaller amounts of the milk, many infants show retention below this minimum. The retention with 400 unit milk is greater than with that of 135 unit milk and is above the calculated minimum for most babies at less than 1.8 ounces of milk to the pound.

In children over 1 year of age, retention of calcium increases with the intake, whether or not vitamin D is given, but the retention is greater with vitamin D. Between 1 and 6 years of age the retention without vitamin D in half of the cases is below the minimum requirement with 750 c.c. of milk, and in the majority of cases is not above it until 1000 c.c. of milk is given. With 340 units of vitamin D daily, the retention in the majority of cases is above the minimum when 750 c.c. of milk is taken, and always when 1000 c.c. is given.

Vitamin D is, therefore, necessary for many children between 1 and 6 years of age. The child over 6 requires

*This and the following abstracts are taken, by permission, from The Borden Digest for October, 1937.

vitamin D to a slightly less extent than the child under 6. With 340 units of vitamin D daily, from 750 to 1000 c.c. of milk is adequate for most subjects, but 500 c.c. is insufficient for most children even when a teaspoonful of cod liver oil is added daily.

ELLIS, L. N. AND ZMACHINSKY, A.

The Sparing Action of Lactoflavin on Vitamin B_1. Science, 86:245, Sept. 10, 1937.

Experiments with laboratory animals showed that the addition of lactoflavin to diets deficient in vitamin B_1 exerted a sparing effect upon this vitamin, since the growth and length of survival of the animals during the period of vitamin B_1 deficiency was directly dependent upon the lactoflavin content of the maternal diet. These results are in agreement with those of other investigators. The sparing action has been found so far to be specific only for vitamin B_1.

The lactoflavin used in the reported experiment was Borden's 1E grade, which is tested free of vitamin B_1 and other water-soluble vitamins. Lactoflavin is now considered to be vitamin B_2 or G.

RAFSKY, H. A.

Non-Surgical Treatment of Pyloric Obstruction Resulting from Peptic Ulcer. N. Y. St. J. M., 37:1539, Sept. 15, 1937.

A series of 26 cases was successfully treated by non-surgical means for the inflammatory type of pyloric obstruction. The methods employed consisted of a gastric lavage of warm water given every day, then every other day, and subsequently less frequently as the patient improved. For five days eight ounces of sweet milk, one-half ounce of sweet cream, and one dram of sugar were given every two hours, and one-half an ounce of olive oil, twice daily. Then two raw eggs or egg-nogs were added. On the sixth day, two ounces of cooked cereal and three eggs were allowed; on the eighth day, four ounces of cereal and two ounces of pureed vegetables; on the tenth day, four eggs; toast was permitted on the twelfth day. Some alkalis, but not in excessive amounts, were also used.

After from 3 to 10 years, twenty patients are still comparatively symptom free.

Pasteurization in England and America. Edit. Am. J. Pub. Health, 27:920, Sept., 1937.

Pasteurization of *all* market milk, says this editorial, is now generally recognized by health and medical authorities, by most of the dairy industry, and by a substantial proportion of the people of this country as an *essential* public health measure. Today, about 88 per cent of the milk supplies in all cities over 10,000 population in this country is pasteurized, although the amount varies in different parts of the country, and the average is brought up by the many larger cities where nearly 100 per cent pasteurization has been attained. In our communities in the 1000 to 10,000 population group, on the other hand, only about 39 per cent of the milk is now pasteurized. These figures indicate that market milk in our large cities is much safer than in the rural sections of the country.

This editorial also expresses the opinion that more certified milk should be pasteurized.

In England, pasteurization has not received as wide recognition as in the United States, although the British public health and medical professions are strongly advocating this desirable process, which they believe should precede much-needed attempts to increase milk consumption in Great Britain. Recent investigations have shown that pasteurization does not appreciably affect the excellent nutritive properties of milk.

"Raw milk, whether in England or America," concludes this editorial, "should no longer be permitted to impede public health progress."

HOY, W. A. AND NEAVE, F. K.

The Phosphatase Test for Efficient Pasteurization. Lancet, 233:595, Sept. 4, 1937.

Since 1935 the phosphatase test has been used to detect the efficiency of pasteurization, the efficacy of the test depending upon the fact that the tuberculosis bacillus is destroyed more quickly than the phosphatase when milk is heated.

The test is valuable in indicating faulty operation of or defects in pasteurizing machinery, and it can also be applied in the case of the high-temperature short-time method of pasteurization.

The survey reported showed that the efficiency of pasteurization in London had been greatly improved during the past two years, especially in the larger firms having their own control laboratories. The test is particularly useful in advisory work in tracking down faults in the functioning of pasteurization.

GRAHAM, S. AND MORRIS, N.

Effect of Boiling on Nutritive Value of Milk. Arch. Dis. in Childr., 12:169, June, 1937.

Metabolism tests on two boys, aged 10½ and 7½, showed that when 50 per cent of the caloric value of the diet and 70 per cent of the protein were supplied by milk, there were no significant differences in the retentions of calcium, phosphorus, and nitrogen when raw milk and boiled milk were given. The results indicate that there is no evidence that over short periods the boiling of milk impairs either its absorption or utilization, when there is an ample supply of proximate principles and minerals, and the caloric intake is adequate.

KOBER, L. R.

Undulant Fever Therapy: Excellent Results From Typhoid Vaccine Intravenously. S. W. Med., 21:817, Sept., 1937.

Successful treatment of 7 cases of undulant fever with foreign protein shock therapy, in this instance typhoid vaccine administered intravenously, is reported by the author. This method was used for strong and healthy patients, but in those who are seriously debilitated or suffering from complications, less severe reactions are obtained with intramuscular or subcutaneous injections of melitensis vaccine.

MCLESTER, J. S.

Nutrition Problems in Education. J. A. M. A., 109:838, Sept. 11, 1937.

Since good nutrition is a prerequisite to health, and the healthy child can make the best use of the education offered him, every effort must be made to see that all school children are properly nourished.

Nutritional failure is seldom simple or complete, but is generally multiple, incomplete, and correspondingly complex. The vague borderline case of nutritive failure of mild degree is the most interesting, and such cases are the most frequent. The prime duty of the school physician is to recognize disorders of this type and to correct them.

The school must endeavor not only to correct these defects, but to enhance the development of the normal child by having him reach optimum instead of merely adequate nutrition. To do this requires education of the pupil, the parent, and the teacher. The greatest energy should be expended not on individual, selected children, but upon the student body as a whole.

Emphasizing the essential nature of any one food factor or group of factors is dangerous, except in the case of milk. "Because of its importance to the child," declares the author, "I think it proper to emphasize time and again the great value of milk.

The nutrition class is of great educational value, not only because of its help to the undernourished pupil, but for its influence on the dietary habits of all students. The example set by the lunch room is likewise of great help to teachers who are giving broad instruction in nutrition.

COWELL, S. J.

The Physiological Bases of Nutrition. Brit. M. J., p. 406, Aug. 28, 1937.

The British Medical Association has

a Section of Nutrition. Its scope, said the author in an address at the last annual meeting, should be wide enough to cover a large part of the field of medicine, and indeed it is already capable of so doing.

In discussing the practical aspects of nutrition, it is pointed out that milk-feeding tests on children have demonstrated that the mean rate of growth can be accelerated with this valuable food. Dental caries can also be prevented by dietary means, and infections reduced by proper nutrition.

Optimal nutrition can be secured by increasing the intake of such protective elements as safe milk and other dairy products, all kinds of vegetables, especially green vegetables, eggs, fat fish and liver. Such protective foods are essential for pregnant and lactating mothers and for growing children, all of whom must have a liberal allowance of milk.

COKE, E. C.

Plans of the Chilean Government for Improving the Nutrition of the People. U. S. Pub. Health Reps., 52:1150, Aug. 20, 1937.

In outlining the problem of nutrition in Chile, and the Government's plans for its improvement, the Minister of Health states in this article that the most serious and immediate problem is that of overcoming a gradual decrease in milk production, already below the minimum needed. Milk, he says, is the principal material for the building of a race, irreplaceable in nearly all cases by any other food, and the most important of the protective foods.

Milk has, furthermore, "an inhibitory action on precocious sexual development," according to studies of the author and his co-workers.

The Government is stimulating milk production and consumption by purchasing milk for school lunches, and by lending capital at low interest to the dairy industry.

GODBOLE, N. N.

Milk. The Most Perfect Food. Chemical Publishing Co. of N. Y., Inc., p. 138, $2.50, 1936.

The professor of industrial chemistry of Benares Hindu University in India has prepared this text in English for the purpose of disseminating correct knowledge of milk as "the most perfect food." As a factor in promoting necessary consumption of milk and dairy products in India, this creditable treatise should serve a useful purpose, and it should also be of interest to those in this country who are directly concerned with the production and distribution of milk, generally known in the United States as "our most nearly perfect food."

The book begins with some interesting references to milk from ancient Vedic and Ayurvedic literature; then presents statistics on milk imports, production, and use in India and elsewhere; discusses the composition and nutritive properties of milk and dairy products, and their influence on health; presents arguments in favor of a vegetarian diet; discusses tea, coffee, cocoa, tobacco and alcoholic drinks; and concludes with some comments on the medicinal properties of milk, and on breeding and feeding.

There is a vigorous foreword by Pandit Madan Mohan Malaviya, an extensive table of food analyses, and a good index. The book is an interesting contribution to the international literature on milk.

MEANS, J. H., HERTZ, S. AND LERMAN, J.

Nutritional Factors in Graves Disease. Ann. Int. Med., XI, 429, Sept., 1937.

The thesis of this presentation is that malnutrition may cause or at least precipitate thyrotoxicosis. The material that forms the basis of their observations came from the Thyroid Clinic of the Massachusetts General Hospital and covered a total of 35 cases. Fourteen of these presented a thyrotoxic loss of weight following in the course of attempts at reduction in overweight cases. The remainder of the series presented malnutrition as the result of a variety of conditions other than deliberate efforts at reduction of obesity. In presenting their thought on malnutrition the authors have endeavored to distinguish between what they call general malnutrition, the result of a total negative unit balance, and specific types of malnutrition.

Myasthenia is listed as a common manifestation in Graves Disease. Among other manifestations of general muscle weakness they offer the rather interesting thought that exophthalmus may be merely a local expression of a general muscle weakness. The degenerative changes in the striated recti muscles contrasted with the normal appearance of the smooth muscle of the eye is offered as a suggestion that a muscle imbalance obtains which results in exophthalmus. Decalcification of the bones is listed also as a specific form of malnutrition. They suggest that while thyroid secretion causes a definite increase in the rate of removal of calcium and phosphorus from the bones, it differs definitely from the influence of the parathyroid hormone in that there is no significant increase in the blood calcium and blood phosphorus in the latter condition. They believe that the marked withdrawal of these chemicals is a specific influence of hyperthyroidism and not the result of an accelerated metabolism. They observed in a few cases of long standing thyrotoxicosis a rather marked osteoporosis of both the spinal vertebrae and of the long bones and call attention to one case particularly in which there was found a compression fracture of a lumbar vertebra the result of osteoporosis. This patient recovered symptomatically, though without much evidence of recalcification from an X-ray standpoint, on a high calcium diet and Viosterol. They found a subnormal hemoglobin value in a rather large per cent of their cases. These patients presented the tongue and low hydrochloric acid content, with the characteristic male changes of a hypochromic anemia. A satisfactory restoration of the blood iron was obtained under a regime of iodine and iron. Whether there is avitaminosis in these cases of Graves disease is discussed. They noted an improvement in appetite and a gain in weight in some of their cases of thyrotoxicosis when fed Vitamin B but no change was noted in the basal metabolic rate. The role of Vitamin B in thyrotoxicosis is suggested, but an evaluation of its real influence was fogged by the simultaneous administration of iodine. They urged that in the preparation of a thyrotoxic patient for operation that saturation with iodine is not sufficient, but that the general nutrition should be improved with reference to specific deficiencies.

In their conclusions they warn against a too vigorous reduction of the gland in obese patients and suggest that thyrotoxicosis may be induced thereby. They believe that a high protein diet is undesirable in the preparation of the thyrotoxic patient for operation on the ground that the specific action of protein is to increase metabolism. They prefer to rely more exclusively upon carbohydrates. Their attitude toward fat content of the diet is a neutral one. While recognizing that unnecessary delay in the thyrotoxic patient in securing operative relief should be avoided, yet they hold that there is a tendency of the surgeon to operate before the evidences of malnutrition, as well as the cardiac insufficiently, have been adequately cared for.

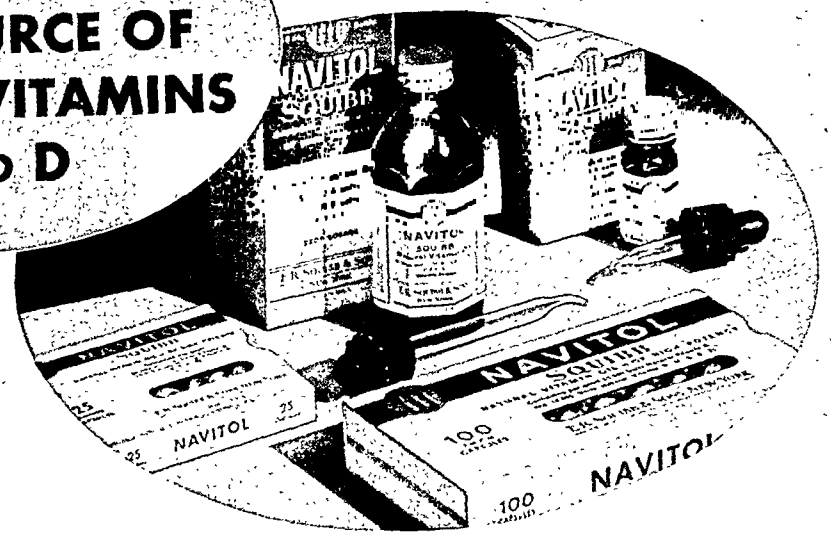
Virgil E. Simpson, Louisville.

ALVAREZ, W. C.

New Light On Intestinal Peristalsis in Health and Disease. Proc. Staff Meetings Mayo Clinic, 12:657-660, Oct. 20, 1937.

The author reports on some work which has been in progress over a period of several years. He concludes that there are two separate systems of nerves regulating the small bowel activity, one consisting of long nerves uninterrupted by synapses, very resistant to anoxemia and nicotine, and believed to mediate the impulses that are

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responsible for so-called systolic contraction of the small bowel, the other a system of short nerves interrupted by synapses, sensitive to nicotine and anoxemia, and believed to preside over the coordinated peristaltic rushes. He feels that during life and health the synaptic nervous system of the bowel and the extrinsic nerves are constantly supplying the muscle with some sedative which keeps the fibers from responding strongly to every stimulus that arrives by way of the long unbroken nerves.

A possible explanation for gas pains and failures of peristalsis in persons subjected to adverse influences is offered on the basis of loss of the normal quieting nervous mechanism thus leaving the bowel at the mercy of the stream of stimuli arriving by way of the hardy long tracts. At present there is no known specific remedy for such conditions.

Hanes M. Fowler, Fort Wayne.

LINDSAY, J. W., RICE, E. CLARENCE, SELINGER, MAURICE A. AND MISH, K. HAMMOND.

Protamine Insulin as a Contributing Factor in the Death of a Diabetic Patient with Cerebral Arteriosclerosis. Ann. Int. Med., Vol. 10, June, 1937.

The authors present a case of fatality of a diabetic patient treated with protamine insulin.

Here the difficulties in the control of the patient's diabetes were reduced, however reactions attributed to insulin hypoglycemia were accentuated, with death resulting from a severe hypoglycemia from the cumulated effects of the insulin.

The patient, an unmarried white female, developed diabetes mellitus in 1931 at the age of 44. Up to August, 1933, when she came under observation, she had lost 71 pounds.

Treatment with varying doses of ordinary insulin and varying diets during and after hospitalization never satisfactorily controlled the diabetes. Occasional insulin reactions were experienced with an attack of coma in October, 1934.

Protamine insulin was started on April 1, 1936, with immediate improvement. Because of economic circumstances the patient was unable to maintain proper contact with the clinic.

On September 3, 1936, she was found unconscious in bed and removed to the hospital with a tentative diagnosis of coma due to hypoglycemia. She remained comatose and died eight days later. At necropsy most striking changes were found in the brain, exhibiting marked arteriosclerosis.

The history obtained from the patient's relatives and friends indicates she probably experienced the effects of a low blood sugar on a number of occasions over a period of 2 months preceding death.

Because of the possible dangers incident to the use of any insulin preparation with prolonged action and cumulative effects, the authors feel that their use should be restricted to those who can be kept under constant control.

The medical treatment with accompanying tables of diet and insulin before and during hospitalization is discussed.

B. B. Vincent Lyon and Nathan A. Noble.

NICHOLS, BERNARD H.

Roentgenology as an Aid to the Diagnosis of Lesions in the Upper Right Abdomen. Jour. Ind. State Med. Assoc., 30:565-567, Nov., 1937.

In cases where there is uncertainty as to the exact type and location of lesions in the upper right abdominal quadrant the radiologist should be approached as a consultant and he should determine the type and method of examinations necessary to obtain the most satisfactory explanation of the patient's symptoms. Too often the radiological examination is useless because some specific procedure was ordered which was entirely inadequate to establish the correct diagnosis.

The frequency of need for exploratory operations has lessened with advance in radiology.

A 14 x 17 film of the abdomen permits examination of the spine, pelvis and abdominal organs which includes the kidneys, ureters, bladder, liver and spleen. This examination should be carried out before any opaque media is introduced into the circulation or abdominal organs.

Lesions of the spine include, arthritis, postural defect, neoplasm of the bony spine or spinal cord, fracture, dislocation, or ruptured nucleus pulposus. Calcific deposits in the abdomen may be due to kidney stones, ureteral stones, calcified tumor or cyst, calcified gall bladder, gall stones, mesenteric glands, or calcific deposits in the outline of the kidney pelves and calices due usually to old tuberculosis of the kidney. The location of suspicious calsific deposits should be determined immediately. Abnormalities of the kidney as regards size, shape, position and presence of tumors can be determined.

If the foregoing examination reveals no abnormalities then a plain film of the gall bladder region should be made and cholecystographic dye administered to determine the function and presence or absence of non-opaque stones. If the gall bladder is not visualized the dye should be repeated the following night. The administration of barium should then follow with complete study of the stomach and duodenum by fluoroscopy and such films as are necessary and a 24 hour observation to determine the intestinal motility. This is followed by a barium enema and then by air enema if a suspicious lesion is present.

One should not overlook the possibility of gastric crises, angina, or pancreatic disease in cases of upper abdominal lesions. Of course, the radiological examination would not help here.

The author closes with the plea that the roentgenologist be considered a consultant just as any other consultant in medicine and that many satisfactory results will be obtained thereby.

Hanes M. Fowler, Fort Wayne.

ROSENAK, BERNARD D.

Inflammatory Diseases of the Small Intestines (So-Called Regional Ileitis). Jour. Ind. State Med. Assoc., 30:568-572, Nov., 1937.

The earliest cases reported of regional ileitis described the condition affecting the terminal portion of the ileum. Subsequent reports have described the lesions occurring in separate parts of the ileum, the jejunum, the cecum and even the duodenum in a recent case. The pathology of the lesions is that of a non-specific inflammation, involving all layers of the intestinal wall and characterized by early infiltration of the fibroblasts, thus leading to thickening, induration, and stenosis with marked mucosal destruction.

The etiology of the disease is unknown. There is no evidence to substantiate a possible causal relationship to appendicitis or tuberculosis. Bacillary dysentery and long standing functional disorders have been mentioned as possible causative factors but further study is needed for confirmation of such views.

Clinically, the disease is found in young adults in more than half the cases. The outstanding symptom is abdominal pain, usually of a distinctly colicky nature and tending to be present intermittently over long periods of time. Fever is usually present, the type and degree depending upon the condition of the lesion. In the average case it varies between 101 and 103 and is usually constant. Some change in the bowel habits is usually seen and diarrhea is almost the rule. The stools usually number 3 to 6 per day, are semisolid or mushy, and do not contain much mucus or gross pus or blood. Constipation may ensue with the development of the obstructive stage of the disease. Nausea and vomiting are seen occasionally in early cases and more often in later stenotic phases of the disease. Leukocytosis is never extreme in uncomplicated cases, and there is usually a microcytic anemia. Generally the patients present weakness, emaciation, and weight loss in proportion to the duration and severity of the



"The day will come... when all milk will be packed in cans"

Whether or not this prophecy will come true remains to be seen. It is, however, interesting to note that it has been made time and again by prominent physicians.

The basis for the prediction is not, of course, the relative merits of containers—but rather the comparative values of two forms of milk, evaporated milk and ordinary "fresh" milk.

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disease, and are usually apathetic and mentally depressed. The posture and gait may suggest peritoneal irritation. In such cases the suspicion of a small bowel lesion should be readily confirmed by finding a tender mass in the right lower quadrant, but its absence does not entirely exclude ileitis as a possibility in cases presenting such a clinical picture.

The diagnosis is made on the basis of the clinical picture and X-ray findings, using first the barium enema and then the barium meal with frequent observations and films during the eight hours following the meal.

The differential diagnosis is concerned mainly with tuberculosis, Hodgkin's disease and lymphosarcoma, carcinoma, right sided colitis and amebic colitis.

As regards treatment, extensive resection of the involved areas seems to offer the best hope of a lasting cure. Other therapeutic measures that have been advocated are side-tracking operations, and medical treatment with nonroughage diet and anti-spasmodics.

The paper is discussed by Dr. William R. Tindall of Shelbyville.

Hanes M. Fowler, Fort Wayne.

MULHOLLAND, H. B.

Intravenous Liver Extract in the Therapy of Pernicious Anemia. Report of a case. Ann. Int. Med., 11:671-674, Oct., 1937.

A case of pernicious anemia is reported which failed to respond to the administration of oral liver, intramuscular extract, ventriculin, and blood transfusions, but with intravenous liver extract responded with a prompt and complete remission.

The report covers the period from Nov. 19, 1934, up to the time of writing. During this time there were two exacerbations of the condition. The first was marked by a hemoglobin of 22%, red count of 1,900,000 and white count of 3,000. The patient at this time responded satisfactorily to the use of oral and intramuscular liver extract. About one year later he had gradually lost ground until the hemoglobin was 35%, the red count 1,740,000 and the white count 2,800. He was given liver by mouth, iron and ammonium citrate, intramuscular liver extract, ventriculin and blood transfusions over a period of some 50 days, all to no avail. He was then given 20 c.c. of liver extract intravenously which was followed by a chill and a temperature of 101° F. Improvement was seen at once, and with each succeeding intravenous injection (five in all) the reactions decreased in severity to slight flushing of the face and a little shortness of breath. The blood picture returned to normal and the patient is being maintained at home in a good state of health with a normal blood picture by the intramuscular injection of 2 c.c. of liver extract once a week.

The author was unable to find in the literature mention of a similar case of pernicious anemia. He says that one can only speculate as regards the reason for this patient's failure to respond to the ordinary therapeutic measures. He refers to Minot's statement as to the need of adequate quantitative treatment in pernicious anemia and says that that is the possible explanation of the behavior of this particular case.

Hanes M. Fowler, Fort Wayne.

DILLON, EDWARD S. AND DYER, WALLACE W.

Factors Influencing the Prognosis in Diabetic Coma. Ann. Int. Med., 11:602-617, Oct., 1937.

This report is based on the records of 268 cases of diabetic acidosis admitted to the Philadelphia General Hospital during the years 1931 to 1936. Of the 268 cases, 117 died, a mortality of 43.7%.

The cases are classified according to the presence or absence of complicating diseases, and also according to the severity of such complications.

They grouped the cases according to the outcome and correlated these findings with the data obtained upon the patient's admittance to the hospital in an effort to determine what inference regarding prognosis could be drawn from the information obtained within an hour or so after admittance.

The presence of complications is an important factor in determining the prognosis as evidenced by the fact that of 139 cases with complications 85 died, a mortality of 61.2% for that group.

The mortality for all cases in which the blood sugar was above 700 mg. per 100 c.c. was 57.7%, whereas for the cases in which it was 400 or lower it was 29.1%. In the group of uncomplicated cases the average blood sugar for those recovering was 487 and for those who died it was 713. So when the blood sugar is very high a higher mortality is anticipated.

The mortality rate increases with the degree of chemical acidosis as measured by the carbon dioxide combining power of blood. This fact is more clearly evident in the uncomplicated cases.

As the blood urea nitrogen increases above 20 mg. per cent the mortality increases rapidly. In the total series the mortality for cases with 20 mg. and below was 22.1%, whereas for those with more than 20 mg. the mortality was 62.4%. The average blood urea nitrogen for the uncomplicated cases that recovered was 20.5 mg. per cent and for those that died was 44.7 mg. per cent.

There is no correlation between the degree of leukocytosis and mortality. In 191 cases in which a white count was made upon admission it was above 10,000 in all but 16 cases. It usually drops rapidly as treatment progresses.

The total mortality for patients up to 30 years was 16.4 per cent while for those over 50 years it was 74.7 per cent. The average age of those without complications that recovered was 27.1 years and for those that died it was 41.8 years.

As regards sex, the total mortality was 29.6 per cent for the males and 49.7 per cent for the females.

The importance of the mental state as regards prognosis is very great. The total mortality for those patients who were conscious upon admittance was 28.0 per cent and for the unconscious it was 81.0 per cent. In the uncomplicated cases 5.4 per cent of the conscious cases died, whereas 73.0 per cent of the unconscious died.

The length of time the patient has been in acidosis is an important consideration, as the expected mortality increases rapidly with the duration of the acidosis.

The authors conclude that the clinical data are much more important in rendering an accurate prognosis than are the laboratory findings. It is more important to know the complications present, the mental state, the age of the patients, and the duration of the acidosis, than it is to know the blood sugar, the carbon dioxide combining power and the urea nitrogen. The latter factors are indispensable, however, in properly gauging doses of insulin and glucose in treating the patients.

Hanes M. Fowler, Fort Wayne.

GAGE, MIMS.

"The Surgical Treatment of Peptic Ulceration." South. Surg., 6:392-404, Oct., 1937.

In a thoughtful presentation, with an excellent list of references, the author gives an interesting approach to the determination of cases suitable for operation and surgical procedures indicated. The etiological factors most resistant to medical or surgical relief are "tissue susceptibility" and "constitutional predisposition." On the other hand, "hypersecretion and hyperacidity," "focal infection," and "gastric trauma" present factors that can be controlled. Most ulcers will heal if these controllable factors are managed by a rigid medical regimen which includes complete abstinence from tobacco, alcohol, condiments and highly seasoned foods, strict adherence to a bland diet with two-hour feedings, and thorough elimination of foci of infection, especially infected teeth. Chemical alkalies are of insignificant importance as compared with physiological neutralization accomplished by frequent food ingestion and regurgitation of alkaline duodenal secretions. Relief of

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is due to the fact that it supplies in scientific balance the eight essential factors indicated for the treatment of gastrointestinal dysfunction . . . as evidenced by impaired digestion or assimilation, by autointoxication or chronic constipation.



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pylorospasm by the use of belladonna is to be recommended. Injection treatments are useful only in proportion to the psychic effect obtained and the ulcer regimen followed.

Surgical treatment is reserved for the complications which are, in order of importance, perforation, hemorrhage, stenosis, and penetration. Duodenal ulcers are best treated by pyloroplasties (Finney, Horsley, or Judd type) or gastro-duodenostomies (Hoffman or Rienhoff type). These procedures are physiological in that the acid gastric chyme is received by the duodenal mucosa which is resistant to its digestive action rather than the jejunal mucosa which is prone to ulceration. Gastro-jejunostomy is, however, safe and indicated where a chronic cicatrizing ulcer has resulted in gastric retention, gastritis, and hypoacidity. Entero-enterostomy should never be done in conjunction with gastrojejunostomy, or gastric resection either, since it establishes duodenal drainage with the strong probability of ulcer formation.

The surgical treatment of gastric ulcers is demanded by the same indications as in duodenal ulcers plus the ever-present possibility of malignant change. This must be suspected in all ulcers which do not show demonstrable roentgenological evidence of healing under medical regimen. Surgical procedures should accomplish removal of the tissue susceptible area and restoration of the gastro-intestinal opening so that there will be constant reflux of alkaline duodenal juices into the stomach. Gastrojejunostomy, though commonly used, is less effective than a partial gastrectomy. While the Billroth I or Schoemaker's modification are more physiological the Polya modification of Billroth II is the most popular and is very satisfactory technically and therapeutically.

Jejunal ulcer demands surgical treatment which consists of subtotal gastrectomy, resection of the involved segment of jejunum with end-to-end anastamosis and a gastrojejunostomy.

After any surgical treatment the patient should be made to understand that he has an "ulcer diathesis" with no guarantee against recurrence or severe hemorrhage if he neglects controlling the controllable factors.

J. Duffy Hancock, Louisville.

ROUSE, MILFORD O. AND PATTERSON, CECIL O.

"The Clinical Significance of a Mobile Colon." South. Med. Jour., 30:963-968, Oct., 1937.

The usual symptoms of a mobile colon are recurring pain in the lower abdomen, usually on the right side, and obstinate constipation. The actual attack may be confused with acute appendicitis but can be differentiated in a number of ways. There is usually a history of pain and constipation dating back to childhood, attacks of pain most likely occur after several days elapse without a bowel movement or when an unusually large bulk of food has been ingested 6 to 24 hours previously, and relief has been obtained in such attacks by the emptying of the large bowel by purgation, enema, or abdominal massage. As a rule there is no initial epigastric pain, usually no nausea, vomiting, or fever, the white count is not increased, there is no marked tenderness or rigidity at McBurney's point, and the distended cecum and ascending colon may be palpated. If doubt still exists after a cleansing enema exploration should be done rather than risk the danger of overlooking an acute appendicitis. If relief is obtained by the enema X-ray studies can be made later and subsequent treatment determined. If exploration reveals a harmless appendix surgical correction of the anomalous mobile cecum should be done if the case is an extreme one or has resisted adequate medical care. This care consists of increasing the body weight, bed rest in selected cases, abdominal exercises, the wearing of a comfortable abdominal support, tonic physiotherapy and psychotherapy.

Obstipation, frequent abdominal pain

FIRMLY ESTABLISHED ON A SOUND, SCIENTIFIC BASIS

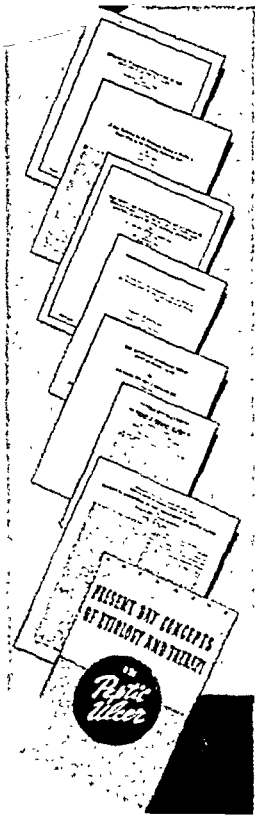
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HAS REVOLUTIONIZED PEPTIC ULCER THERAPY

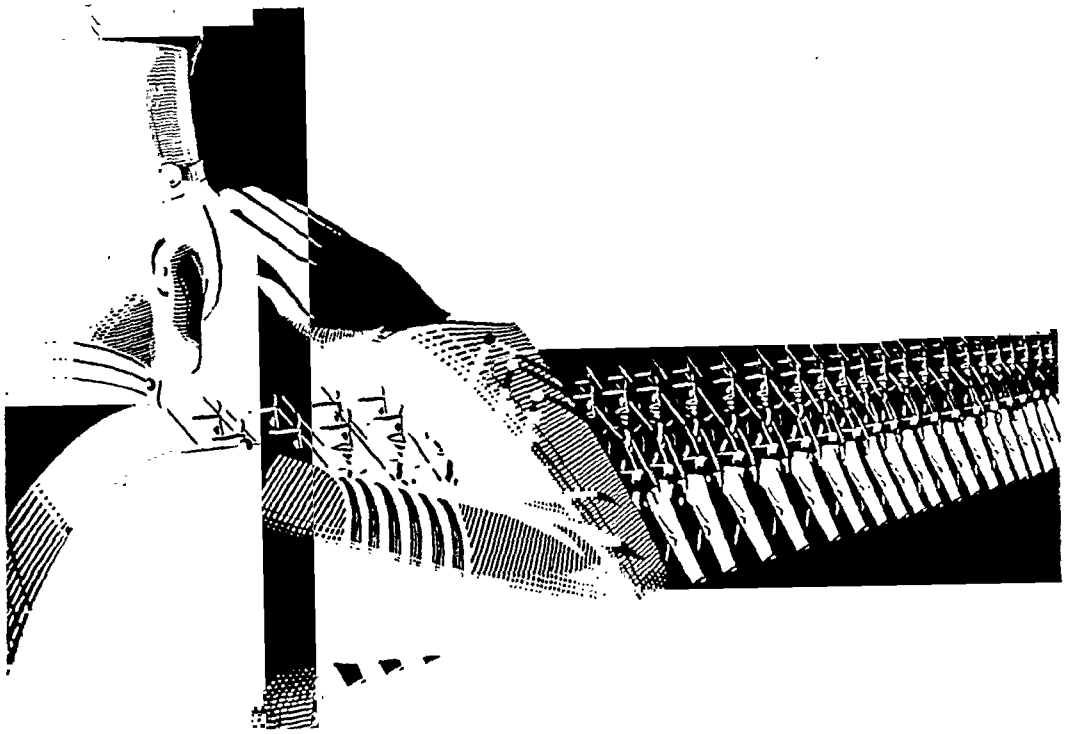
The broad scientific background of Creamalin, based upon published articles, attests the therapeutic efficacy of this unique colloidal cream of aluminum hydroxide. These investigations concur in one important point: that Creamalin induces healing in peptic ulcer with greater rapidity than any other agent heretofore used.

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Petrolagar

of mild intensity, anorexia, malaise, "billiousness," headaches and malnutrition are symptoms that should suggest the possibility of a chronic case of mobile colon.

J. Duffy Hancock, Louisville.

BERNHEIM, A. R. AND LONDON, I. M.

Arteriosclerosis and Thromboangiitis Obliterans. J. A. M. A., 108:2102, June 19, 1937.

The authors report successful treatment of a large number of patients with peripheral vascular disease by means of a diet high in calcium and vitamins, elimination of the use of tobacco, employment of sodium citrate in severe cases, and proper care of the extremities. On this regime 83.8 per cent of 99 cases of arteriosclerosis, and 79.6 per cent of 54 cases of thromboangiitis obliterans showed improvement.

The high-calcium, high-vitamin diet was given because of its favorable influence on vasospasm, but it was also used when the vasospastic element apparently was absent. The chief sources of calcium were milk and cheese, but occasionally calcium salts were employed. Concentrates of vitamins A (19,000 units) and D (1900 units) were added daily, vitamin B was given in the form of wheat germ or yeast, and vitamin C was supplied in orange juice or tomato juice. Lactose was added to the diet of patients suffering from constipation (except diabetics), from 2 to 6 heaping tablespoons a day being effective in the majority of cases.

Sodium citrate was used in severe cases, either by vein or by mouth, in order to reduce the viscosity of the blood. The high calcium diet prevents depletion of the body through sodium citrate, and not only has an anti-vasospastic influence, but produces a beneficial effect on general health. It does not adversely affect the viscosity of the blood, nor does it lead to increased arteriosclerosis.

Other measures, including complete withdrawal of the use of tobacco, freedom from worry, reduction of physical exertion, and thorough care of the extremities are described in detail, and a number of case reports are presented.

THEOBALD, G. W.

Effect of Calcium and Vitamins A and D on Incidence of Pregnancy Toxaemia. Lancet, 232:1397, June 12, 1937.

Fifty pregnant women who were requested to take daily throughout pregnancy 20 grains of calcium lactate, 11,000 units of vitamin A, and 450 units of vitamin D were compared with 50 women whose diet was not supplemented in this manner. All were apparently healthy at the beginning of the experiment. About half of the women in each group were primigravidae, or pregnant for the first time.

In only 13 cases of the 50 women on the high-calcium, high-vitamin diet were toxic symptoms found, whereas 28 of the 50 untreated women showed albuminuria, hypertension, or both. Other symptoms, such as hyperemesis, oedema, headaches, cramps, and insomnia occurred in 21 of the untreated cases, but in only 10 of those receiving calcium and vitamins.

The author believes that the improvement noted was due to the nature of the diet, and that all pregnant women should have these protective substances.

GUNDERSON, F. L.

Nutritional Economics of Dietary Calcium. Am. J. Pub. Health, 27:570, June, 1937.

The daily human need for calcium is widely recognized as ranging from 1.4 to 0.68 grams, or an average of 1.0 gram plus or minus 0.4 gram (expressed as elemental Ca), depending on the age and the needs for growth, pregnancy, or lactation.

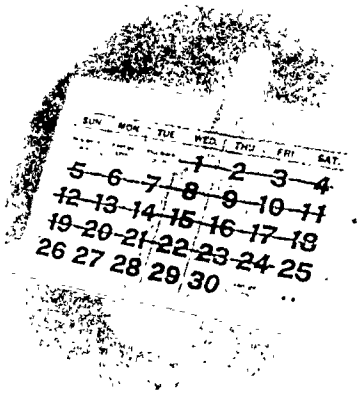
Evaporated milk and American cheese are the cheapest food sources of

SHORTEN

THE

PEPTIC ULCER

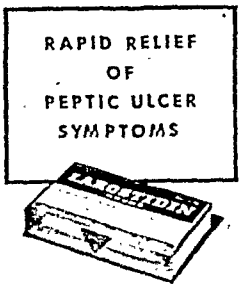
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calcium, since one gram from these products costs only 6.4 cents. Close behind are whole milk at 9.4 cents a gram, and powdered milk at 10.3 cents a gram. A similar amount of this mineral obtained from vegetables or fruits will cost from two to 25 times as much as milk, as shown in a table compiled by the author.

The calcium of milk and dairy products is highly regarded for its biological availability, and these foods also furnish liberal quantities of other important nutrients, such as protein, fat, and vitamins.

Calcium pharmaceuticals cost the consumer from about one to 18 cents per gram of calcium (of lower biological value than that of milk. Ed.). The author suggests that various inexpensive carbohydrate foods might be fortified with calcium salts, a procedure which, with increased milk consumption, would provide more adequate calcium for American diets.

VAUGHAN, W. T. AND PIPES, D. M.

Is There a Correlation Between Food Dislikes and Food Allergy? J. Allergy, 8:257, March, 1937.

Dislike of foods is not correlated with allergy to those foods, according to the authors, who investigated 500 patients by means of questionnaires and followed up 19 allergic cases with skin tests. In only about 20 per cent of the 500 patients with food dislikes was there a correspondence between the dislike and the foods causing the allergic symptoms, while in the 19 tested, there were only 7 instances in which a dislike was accompanied by a positive skin reaction to the food.

In a previous series of 100 cases, it was reported that 46 showed evidence of food allergy, while 66 expressed food dislikes. The 7 foods most frequently disliked were in their order of frequency: spinach, turnips, cabbage, carrot, okra, lamb, and squash. The foods in the same series most frequently found responsible for allergic symptoms were, in order: cucumber, watermelon, raspberry, strawberry, tomato, onion, cabbage and cantaloupe.

The Nutritional Significance of the Curd Tension of Milk. I. The production and properties of "soft curd" milks. J. A. M. A., 108:2040, June 12, 1937. II. The relation of curd tension to the digestibility of milk. J. A. M. A., 108:2122, June 19, 1937.

Newly developed laboratory methods for the quantitative measurement of the curd tension of milk have shown that there is a wide variation in the curd tension of untreated milk from different cows. No precise standard exists at present for a "soft curd" milk. Natural soft curd milk appears to be a less concentrated milk, having a relatively low content of fat, casein and calcium phosphate.

Pasteurization of milk has little effect on the nature of the curd, but softening of the curd may be accomplished by boiling, dilution, addition of acids or alkalis, and the addition of various cereal waters. Homogenization of whole milk usually lowers the curd tension, and commercial methods of preserving milk by evaporating or drying also usually yield a product that exhibits a low curd tension.

The variety of milk preparations that yield soft curds have been shown to be well tolerated and well utilized by infants, children and older persons. Thus, "evaporated, sweetened condensed and powdered milks—all of which usually form soft, flocculent curds—have been used with clinical success in the feeding of normal infants." In general, milk that has a low curd tension leaves the stomach more quickly than milk that does not have this property. Such digestion as takes place in the stomach is more quickly accomplished when the curd is soft.

Numerous references to the scientific literature are included in this report, prepared by the Council on Foods of the American Medical Association.

HARRIS, R. S. AND BUNKER, J. W. M.

The Antirachitic Property of Casein. J. Biol. Chem., 119:XLV, June, 1937.

Rickets could not be produced in rats

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(Alkali Buffers in Palatable Effervescent Solution)

Alka-Vess is preferable to the use of single alkali medication because the presence of buffer salts helps to take up acid in a natural way with less danger of setting up an alkalosis.

The palatability and convenience of Alka-Vess assure regular and accurate dosage.

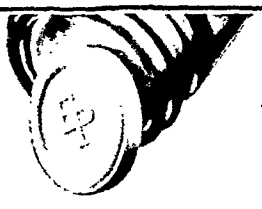
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The CO_2 factor in Aspir-Vess provides brisk effervescence which carries the drug more rapidly through the stomach so that danger of gastric disturbance is reduced to a minimum. Rapid absorption is assured and a maximum clinical effect is secured from minimum dosage.

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DETOXIFIED WITH SORICIN

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B. Coli Vaccine (Merrell), used in conjunction with Soricin Tablets or Soricin Capsules for the treatment of obstinate cases of:

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on diets in which casein from cow's milk served as the protein constituent, even when the ratio of calcium to phosphorus in the diet was 9:1, when the phosphorus content of the diet was less than 0.2 per cent, and when extractable fat-soluble factors were removed from the diet.

BOOHER, L. E.

The Concentration and Properties of Vitamin H. J. Biol. Chem., 119:223, June, 1937.

Vitamin H is defined as a relatively heat-stable component of the vitamin B complex, which is essential for growth and for the prevention of erythredemic dermatosis in rats. It represents the residuum necessary in addition to vitamins B_1 and riboflavin (lactoflavin) to complete the growth-promoting activity of the vitamin B complex.

A 30-fold concentration of this vitamin was extracted from low lactose whey powder containing 5 units per gram, and a 60-90 fold concentrate was obtained from rice polishings containing 12-13 units per gram.

Pasteurization and the Nutritive Value of Milk. Edit. Lancet, 232: 1417, June 12, 1937.

Recent feeding experiments with calves have shown that these animals thrive as well on pasteurized milk as on raw milk, showing no signs of rickets or anemia, and no physical differences on either type of milk.

The dangers of raw milk as a vehicle of infection and the safety given by efficient pasteurization are demonstrable facts that cannot be gainsaid, declares this editorial, which points out that repeated tests have revealed no appreciable difference between the nutritive values of pasteurized and raw milks.

WEISMAN, J. I.

Pasteurized Versus Raw Milk in Undulant Fever. N. E. J. M., 216: 977, June 3, 1937.

In 1930 when the Essex Sanatorium relied in part upon raw milk for its supply, blood tests on 243 patients and employees revealed that 38 or 15.2 per cent contained agglutinins showing the presence of undulant fever. Pasteurization of all milk was then put into effect. Reexaminations of 312 individuals at the hospital, made in 1932, showed that all were negative in titers ranging from 1:25 to 1:200. Included in this group were 23 patients formerly positive with respect to undulant fever.

Pasteurization, says the author, should be made available to 100 per cent of the population, and the public should be educated concerning the dangers of raw milk. All milk cows should be tested yearly for *Brucella abortus* infection and eliminated if found diseased. Contact with the disease is also a source of infection.

Misinformation for the Public. Edit. The Health Officer, 2:6, May, 1937.

"The United States Public Health Service joins with the American Medical Association and the American Public Health Association in condemning *Coronet's* type of gross misinformation on matters vital to the public health," says this editorial in an official publication of the federal government, which thus comments upon "the piece of balderdash" entitled "Is Milk Cancer's Ally?" appearing in a recent issue of the pocket-sized and "pocket-minded" magazine, *Coronet*.

"Let those concerned with public health education, in particular," concludes this editorial, "be alert to the use of dangerous, inaccurate and sensational material having no foundation whatsoever in scientific fact."



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NORMAL
BOWEL ACTIVITY

WITHOUT IRRITANT DRUGS, artificial bulk, roughage or other agents preferably avoided by the Physician.

Restoration of normal physiological bowel activity can be fully expected as a natural result of the combined effects of ZymenoL:

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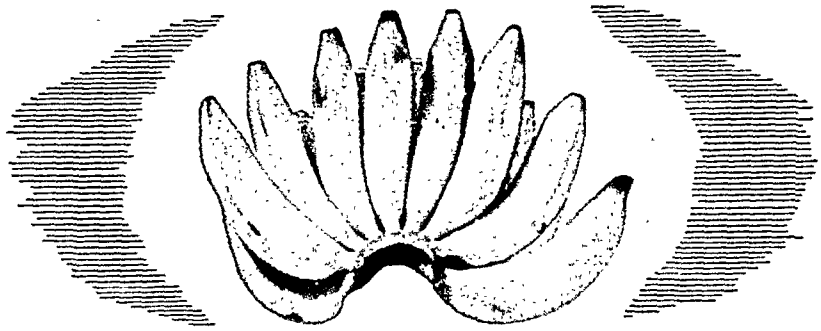
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Because of these attributes, together with their soft fibre, pectins, high content of sugars, satiety value, low content of protein and fat, their vitamins (good source of A-B-C-G) and essential minerals, ripe bananas are prescribed by an increasing number of physicians in many invalid diets, including: ulcerative colitis; peptic ulcer; cardiac; diabetes; liver disorders; nephritis; tuberculosis; as well as in various post-operative and convalescent diets.

In the field of corrective diets, physicians are finding that ripe bananas help combat diarrhea and spastic constipation; also that in combination with milk they constitute a basis for planning a variety of effective, safe reducing diets for persons who are overweight.

LITERATURE ON REQUEST... ADDRESS

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STONE, HARVEY B.

Method of Intestinal Anastomosis with a New Clamp. S. G. O., Vol. 65, No. 3, pp. 383-384, Sept., 1937.

The author describes a new clamp for aseptic intestinal anastomosis. It consists of two pieces, the hinged jaws and compressing handle. Close to the outer surface of each jaw tip a square pyramidal hole is sunk to receive the points of the compressing handle. The compressing handle is made like any forcep but the blades are curved like ice tongs and fashioned to fit the tips of the hinged jaws. The jaws may be secured to the compressing handle as a straight instrument or at right angles to either side.

Five figures illustrate the clamp and show its dimensions and how it may be used.

N. M. Percy, Chicago.

SOMMER, H. AND MEYER, K. F.

Paralytic Shell-Fish Poisoning. Arch. Path., 24:5-360, Nov., 1937.

From the author's summary of a further detailed study of paralytic shell-fish poisoning, the following data of important interest to all medical readers are noted. The authors tabulate and discuss 243 cases of paralytic shell-fish poisoning, with sixteen deaths that occurred between Ventura County, California, and Juneau, Alaska, from 1927 to 1936. Of these, 234 cases were caused by the coast mussel. Nine cases were caused by the Washington clam. They worked out methods for the detection and the quantitative estimation of the poison in shell-fish. Toxin curves for these nine years were constructed from the analyses of mussels collected from many places along the California-Oregon coast; and curves for mussels, sand-crabs and Washington clams from localities near San Francisco obtained since 1931 are detailed. The poison has also been found in small quantities in seven species of edible clams in addition to the shell-fish mentioned.

Poisonous mussels can not be distinguished from non-poisonous ones except by animal test. They never show increased toxicity in the laboratory, but usually show detoxification at a given rate. They may take up poisons from sea water, and evidence is presented which points to the water of the open ocean as the carrier of the poison. As the latter is absorbed by the silicates of the sand, it is not likely to occur free in the water itself. During the poison season it has been found in the residue from filtration of sea water. Whether it is contained in the plankton or in the microscopic sand is not at present decided.

Four different principles toxic for mice have been demonstrated in alcoholic-acid extracts of shell-fish and plankton.

The authors discuss briefly measures for the prevention of shell-fish poisoning and state that thus far treatment of poisoned individual must be purely symptomatic.

N. W. Jones, Portland.

MENNE, F. R., BEEMAN, J. A. P. AND LABBY, D. H.

Cholesterol-induced Arteriosclerosis in Rabbits, with Variations Due to Altered Status of Thyroid. Arch. Path., 24:5-612, Nov., 1937.

The authors report a study of the effects of alterations in metabolism, as produced by changes in thyroid function, on the deposition of cholesterol in the arteries of rabbits fed large amounts of cholesterol over comparatively long periods of time. Observations were made under different conditions, namely (a) normal conditions (controls), (b) following thyroidectomy and after administration of iodine to inhibit thyroid function, and (c) during administration of dessicated thyroid in such a manner as to produce

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gives ALL the advantages of the alkaline antacids without their disadvantages. How? Tri-Calsate is a powerful neutralizer of gastric HCl but does not cause a rebound in acidity nor alkalize the stomach contents. The buffering effect of its end salts protects against a harmful alkalosis, thus eliminating a major disadvantage of the alkaline antacids.

As no carbon dioxide is evolved during the reaction in the stomach, gastric distention and belching are eliminated.

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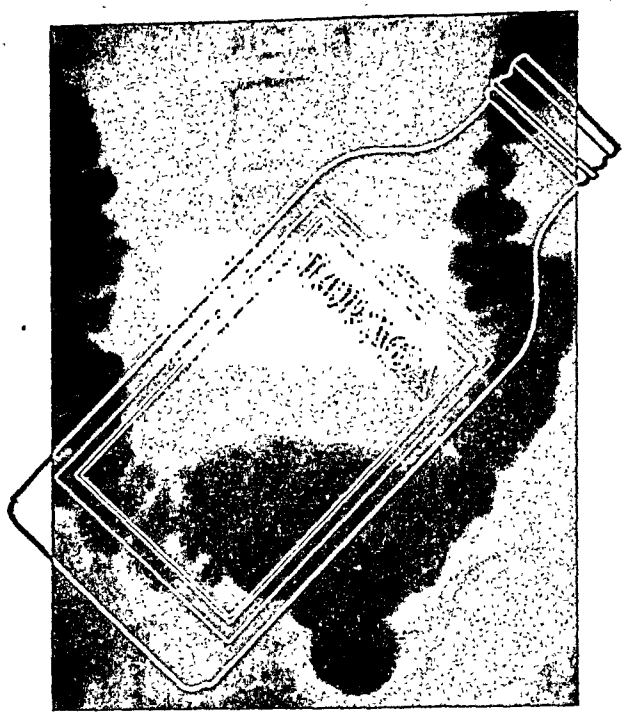
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William R. Warner & Co., Inc., 113 W. 18th St., New York City

intermittent periods of progression and regression in metabolism.

Experimental arteriosclerosis was observed in all groups but it was more marked in those rabbits in which the metabolic rate had been depressed. The authors were led to believe by their studies, as other workers in experimental cholesterol arteriosclerosis in rabbits have been, that the two primary conditions necessary to the development of atherosclerosis are (a) an excess of cholesterol or of cholesterol esters in the blood, and (b) the stress due to mechanical factors of the circulation. The authors recognize the complexity of the problem of human atherosclerosis, but believe these two factors are dominant in the etiology of the latter condition.

There are many discrepancies which naturally must be explained, and the reviewer is inclined to remind his readers that some investigations of human atherosclerosis have shown no correlation between the concentration of cholesterol in the blood serum and the lipid content of the aorta; that the incidence and severity of atherosclerosis are not directly affected by the level of cholesterol in the blood serum.

(Lande and Sperry, *Arch. Path.*, 22:3, 302).

N. W. Jones, Portland.

SOMMER, H., WHEDON, M. A., KOFOID, C. A. AND STOHLER, R.

Relation of Paralytic Shell-Fish Poison to Certain Plankton Organisms of the Genus Gonyaulax. Arch. Path., 24:5-537, Nov., 1937.

The above study is one of a series of studies on shell-fish poisoning by K. F. Meyer and Associates of the George Williams Hooper Foundation, University of California.

The authors in this paper give a detailed biological, chemical and epidemiological study of the shell-fish poison from plankton and methods for its extraction and demonstration. Frequent samples of plankton collected during the summer of 1935 yielded amounts of poison roughly proportional to the numbers of the dinoflagellate Gonyaulax Catenella present. On an average 3000 of these organisms yielded 1 mouse unit of poison. The facts point to certain species of the genus Gonyaulax as the source of paralytic shell-fish poison. Other toxic substances in the plankton may be present.

(Plankton—a zoological term for the floating or drifting organic life of the sea, as distinguished from the coast or the bottom forms of sea life).

N. W. Jones, Portland.

BEHREND, MOSES.

Carcinoma of Colon. Treatment Depending on Location of Lesion. S. G. O., Vol. 65, No. 4, pp. 505-514, Oct., 1937.

As a matter of fact, the author states, there are no specific signs which would lead one to suspect the existence of a grave lesion of the colon early in its course. Any change in bowel habits must be looked upon with grave suspicion. The author is of the conviction that some types of carcinoma of the colon exist and cause symptoms for five years before they are diagnosed. The majority of carcinomas of the colon are found in the sigmoid, recto-sigmoid junction, and rectum. Carcinoma of the colon is definitely not a disease of the aged; no age group seems exempt from it. Males, generally speaking, are more prone to it than females.

Digital, sigmoidoscopic and X-ray examinations of the colon should be made in suspicious cases. Digital examinations should be made in several positions. While carcinoma may be present in multiple parts of the colon, it is uncommon.

Gently Laxative





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THIS STUDY SHOWS THAT OVALTINE ALONE, OF ALL THE THINGS TESTED, IMPROVED THE *QUALITY* OF SLEEP

Three years ago an extensive investigation was begun at a well known University, to determine the influence of certain factors on sleep. 36 men and women were used as subjects in this study, which extended over a total of 6,800 sleep nights.

A wide variety of different factors were tested for their effect on sleep. One phase of the general problem was to study the influence of sandwiches, hot milk, two barbiturates, and Ovaltine. (Ovaltine was included in the study at the recommendation of the investigators.)

Statistical evaluation of the results shows that Ovaltine was the only test procedure which improved the quality of sleep. *It decreased the amount of tossing and turning during the night.* (Motility, i. e., movements during sleep, is recognized as an objective criterion of the restfulness of sleep). In addition, *Ovaltine caused an increase in the number of mornings when the subjects reported they felt well rested on awakening.* These results were obtained when Ovaltine was taken hot or cold, with water, or milk, thereby indicating that it was Ovaltine itself that caused the improvement in sleep.

Ovaltine was the *only* test procedure that accomplished these two favorable results. Sandwiches had no effect on the quality of sleep. Hot milk had no effect except to increase the amount of dreaming. The two barbiturates used gave the effects for which they are known—one a quick sedative action and the other a prolonged depressant effect. But neither drug improved the quality of sleep as did Ovaltine.

These findings with Ovaltine are merely confirmation, from a new and scientific method, of facts long known about Ovaltine. The experience of medical men established the use of Ovaltine for sleep many years ago.

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The author is of the opinion that powerful deep X-ray therapy in these cases does more harm than good.

Pre-operatively the bowel should be cleansed with castor oil and later warm enemata while the patient is on a non-residue diet. Infusions of glucose are given as needed. All cases are digitalized pre-operatively. This does no harm and frequently has been beneficial in the author's experience.

Immunization by intra-peritoneal vaccination is of very questionable value in the author's opinion.

Spinal anesthesia is the anesthetic of choice in all cases. In over 300 cases the author has not had a single death from the use of neocaine.

Wherever the Mikulicz operation can be performed it is undoubtedly the safest to do. Primary colostomy and anastomoses as secondary procedures are appropriate in certain instances.

Infection by the colon bacillus is the bete noire of operations upon the large bowel and to some degree complicates the course of every patient operated upon. Because of the frequency of late infections in the groins the author now makes a separate incision and drains that area. Drainage of the pelvis is also instituted following operations on the sigmoid and rectum.

The author's mortality has been about ten per cent. Sixteen figures and a bibliography accompany the article.

N. M. Percy, Chicago.

CAREY, J. B.

Gastroscopic Observation of the Post-operative Stomach. S. G. O., Vol. 65, No. 4, pp. 447-452, Oct., 1937.

The author proposes the use of the gastroscope as a means of determining precisely the condition of the stomach pre-operatively and post-operatively in those cases with a recurrence or persistence of symptoms. The presence of unabsorbed suture materials and the types and degrees of gastritis common in the post-operative stomach may be seen. Superficial erosions and hyperrugation may be readily seen by the gastroscope, whereas the X-ray examinations for those conditions is notoriously difficult.

Because of the similarity of symptoms and often of roentgen findings in peptic ulcer and chronic hypertrophic gastritis, is is suggested that gastroscopy should always be done in such cases before operation.

Fifteen case reports, six figures, and a bibliography accompany the article.

N. M. Percy, Chicago.

FELLER, M. K., COOK, D. D. M., WALTER, OTIS M. AND ZHITNOFF, N.

Enterectomy in the Surgical Treatment of Hepatic Cirrhosis or Portal Obstruction with Ascites. S. G. O., Vol. 65, No. 30, pp. 331-335, Sept., 1937.

Fuller and Cook, reasoning that if a diminished volume of blood is required to pass through a cirrhotic liver, there may be less ascitic fluid formed, proposed obliteration of a portion of the portal bed to accomplish that end. This smaller volume containing a higher concentration of ostomically active particles should tend toward a slower absorption of water into the capillary bed and furnish a venous volume more concentrated and less in fluid volume.

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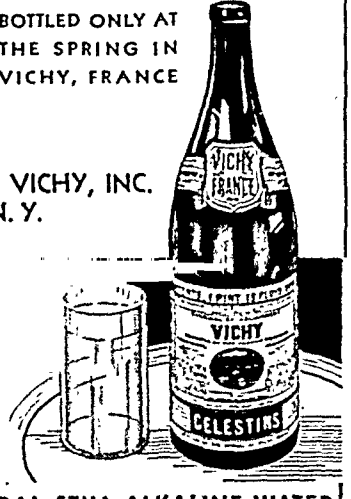


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stantly diminished until it ceased forming entirely. The patient has now been free from ascites for 29 months and has resumed a fairly normal life, which he could not do before operation. No dietary restrictions are imposed and the patient has no diarrhea.

One table and a bibliography accompany the article.

N. M. Percy, Chicago.

MILLER, GAVIN.

Subtotal Gastric Resection for Peptic Ulcer. S. G. O., Vol. 65, No. 4, pp. 489-494, Oct., 1937.

The author discusses gastric resection from the standpoint of mortality and enumerates some aids in reducing that mortality. He observes that the more widely practiced such a difficult technical procedure becomes the less satisfactory the results will be.

If a heart, lung or kidney condition exists, making operation an unduly dangerous procedure, it should not be undertaken. Blood transfusion should be given for any degree of anemia. Infusions of glucose should be given preoperatively in order to build up a sufficient glycogen reserve.

Local anesthesia or spinal anesthesia with splanchnic block are followed by less shock.

The author prefers a high midline incision because less blood is lost; it allows ample exposure, and may be closed securely. If no ulcer is found a pyloroplasty may be done, if pylorospasm is thought to be the cause of the symptoms. Care should be taken to leave the blood supply of the omentum intact; a large omentum without blood supply may be a cause of shock later. The end of the duodenum should be inverted and placed retroperitoneally and then covered with a piece of omentum. This, the author believes, is very important since it tends to localize any leakage from the duodenum. As the jejunum is brought through the mesocolon, care should be taken to avoid kinking or twisting it in any way. A no-loop type of anastomosis following the Hofmeister Finsterer modification of the Billroth *II* operation is performed. The "fatal angle" is reinforced by Finsterer's angle suture. The right edge of the slit in the mesocolon is sutured to the anterior wall of the stomach. Throughout the anastomosis the locked stitch, or the baseball stitch, are used to reduce hemorrhage.

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The author prefers the Hofmeister Finsterer Modification of the Billroth *II* operation over the Polya type because he believes that after the latter

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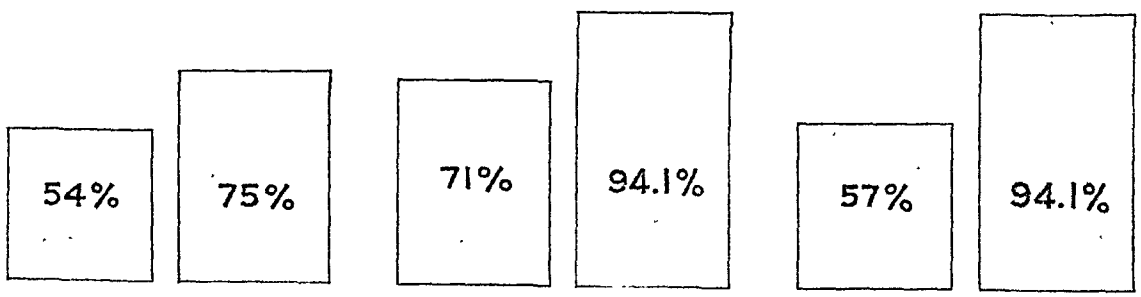
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N. M. Percy, Chicago.

PEMBERTON, JOHN DeJ. AND WAUGH, JOHN M.

The Elliott Treatment as an Adjunct to Operation in Sigmoidal Diverticulitis. S. G. O., Vol. 65, No. 2, pp. 249-251, Aug., 1937.

The authors report a case of sigmoid diverticulitis with vesicosigmoided fistula which was treated by colostomy and later resection by the method of Mikulicz. A transverse colostomy was made and the patient was allowed to rest for about five months, during which time the inflammatory mass did not decrease in size. Elliott treatments were started rectally and were continued at average intervals of one day for 13 treatments. After two weeks the mass had decreased appreciably in size and resection was carried out successfully.

N. M. Percy, Chicago.

GLENN, FRANK.

Total Gastric Resection — An Experimental Study. S. G. O., Vol. 65, No. 4, pp. 540-544, Oct., 1937.

In order to overcome some of the difficulties and unsatisfactory results encountered in total gastric resection the author has devised a new operation for total excision of the stomach, and has practiced it on twelve dogs. The operation is performed in two stages. In the first stage a loop of jejunum is brought up and sutured to the posterior wall of the esophagus and the crura of the diaphragm. An entero-anastomosis is then made between the two limbs of this loop of jejunum and the abdomen closed.

Two weeks or more later the second stage is performed. The abdomen is opened through the same wound and the stomach is cut off just distal to the esophagojejunal approximation. The anastomosis between the esophagus and duodenum is then completed and the stomach is excised by cutting across the duodenum. The stump of the duodenum is then inverted and the abdomen closed without drainage.

Three of the animals died of peritonitis. Those who survived seemed to develop a marked anemia.

From these experiments the author gains the impression that the esophagus lends itself less well to anastomosis than any other part of the intestinal tract and any suturing of the lower end of the esophagus must be done with meticulous care. Motion of the diaphragm disturbs the relations at the lower end of the esophagus.

Eight figures accompanying the article illustrate the operation and show some results.

N. M. Percy, Chicago.

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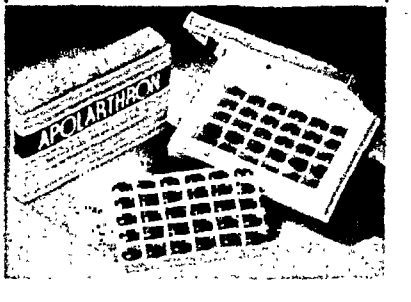
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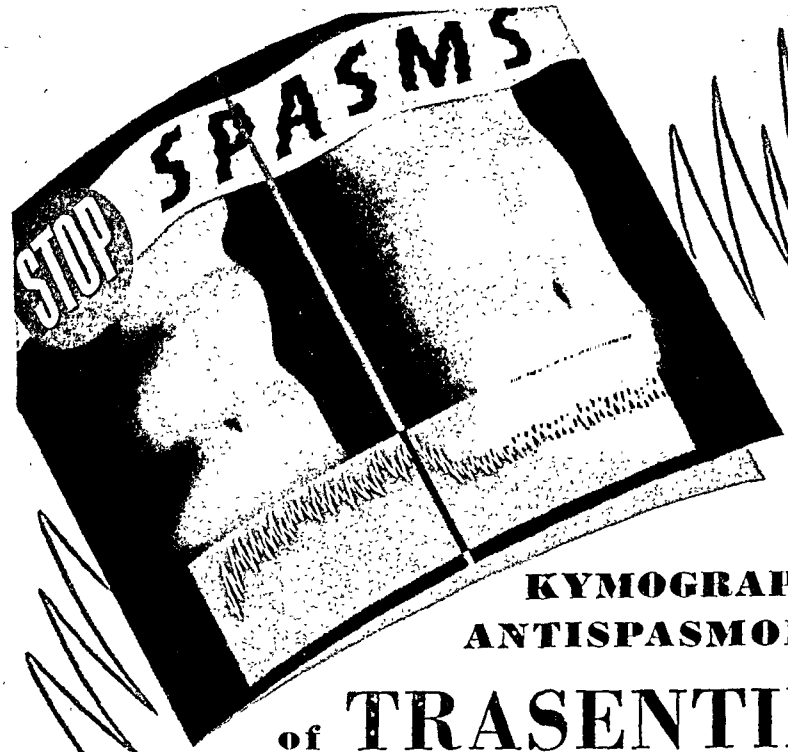
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*J.A.M.A., Jan. 8, 1938; Ceder & Zon, Pub. Health Rep., Nov. 5, 1937.

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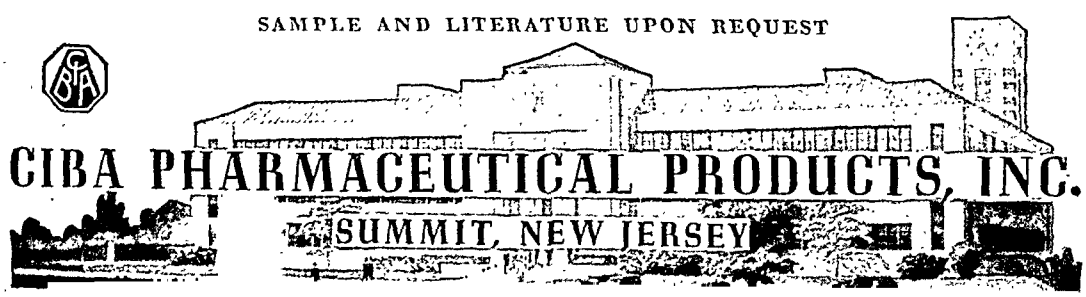
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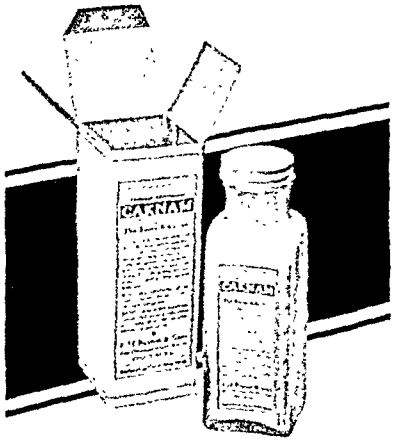
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Volume IV.

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